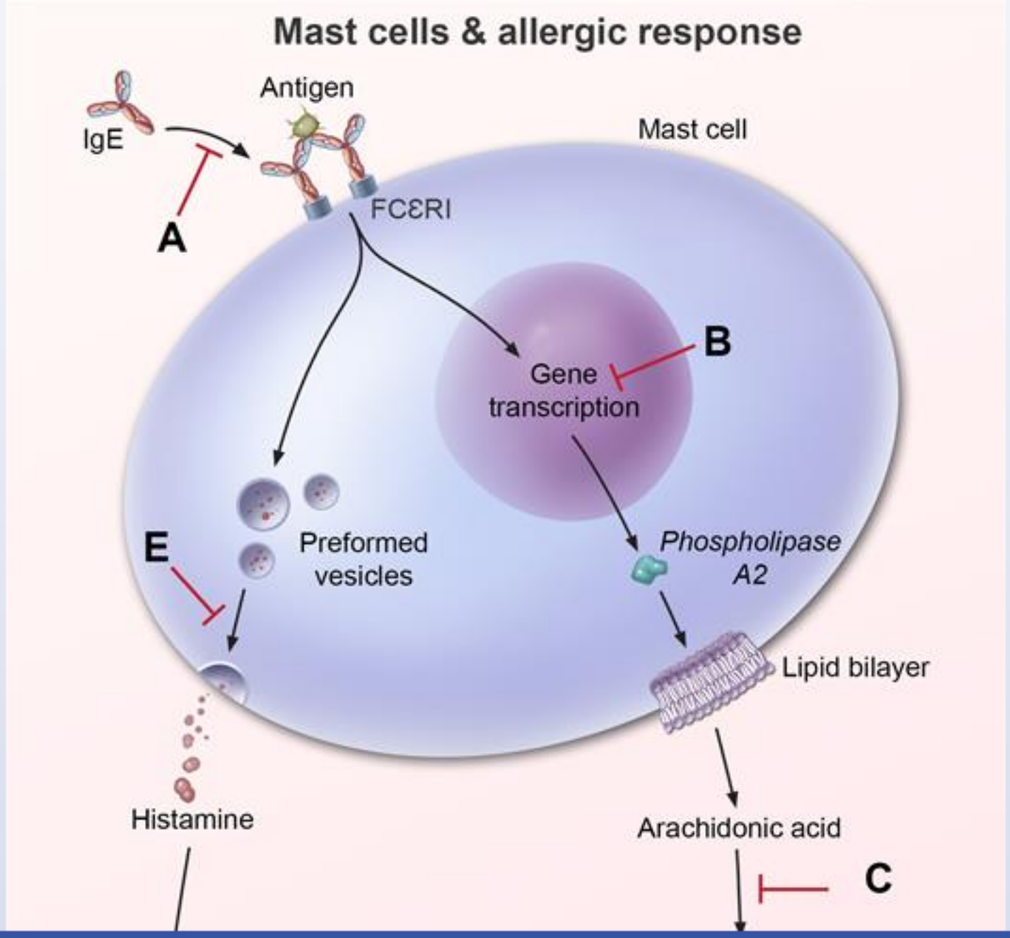
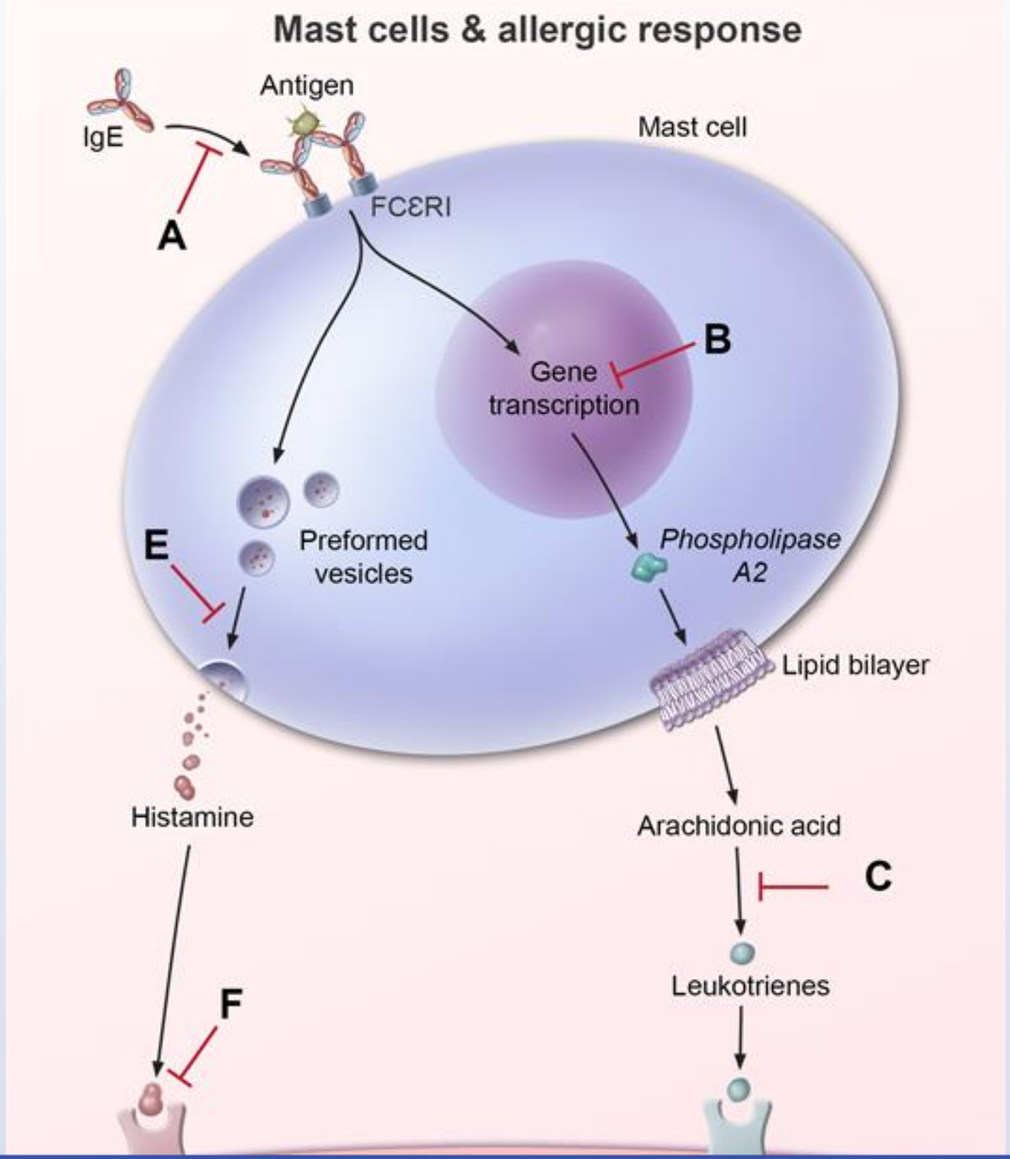
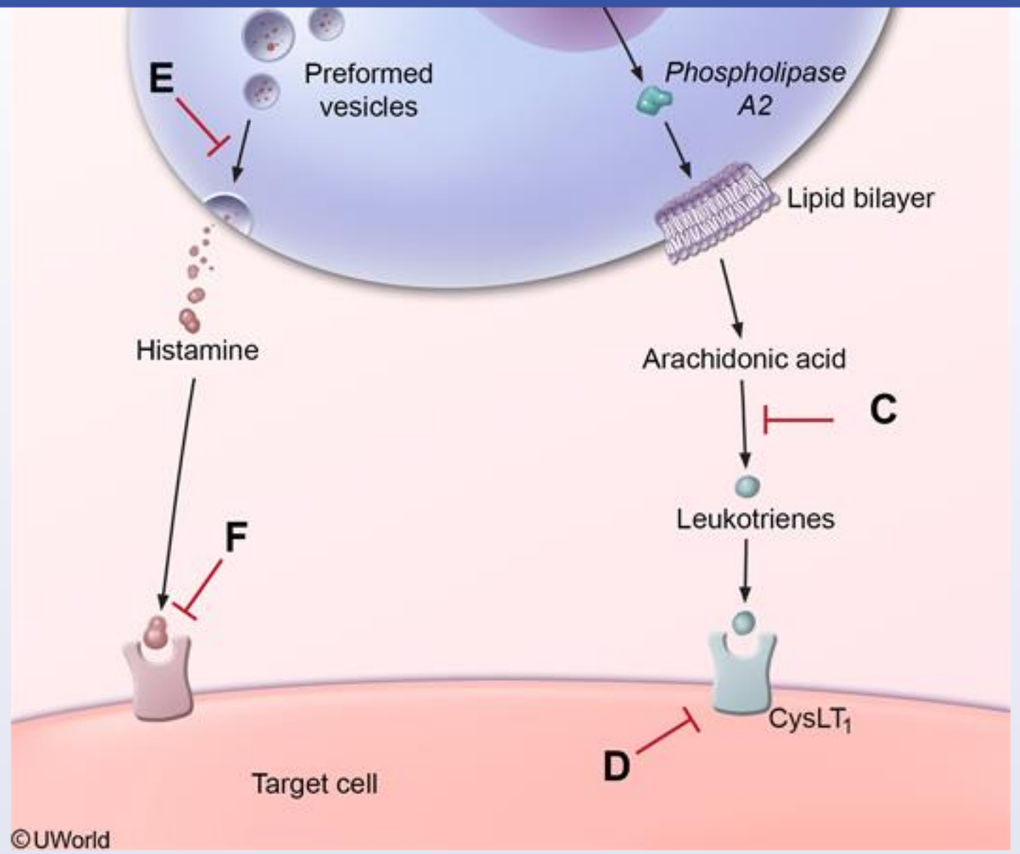
A 10-year-old boy with a history of mild, persistent asthma is brought to the office for follow-up. His asthma symptoms are controlled with an inhaled beta-agonist and inhaled glucocorticoid therapy. There is no family history of asthma, but both his parents and older brother have short stature. The patient's mother is concerned about the use of glucocorticoids because she read on the Internet that they cause growth retardation. The patient's glucocorticoid medication is stopped, and he is started on a trial of inhaled cromolyn. Which of the following is the most likely site of action of this new medication?



action of this new medication?




E
Preformed vesicles
Phospholipase A2
Lipid bilayer
Histamine
Arachidonic acid
C
Leukotrienes
F
CysLT1
D
Target cell
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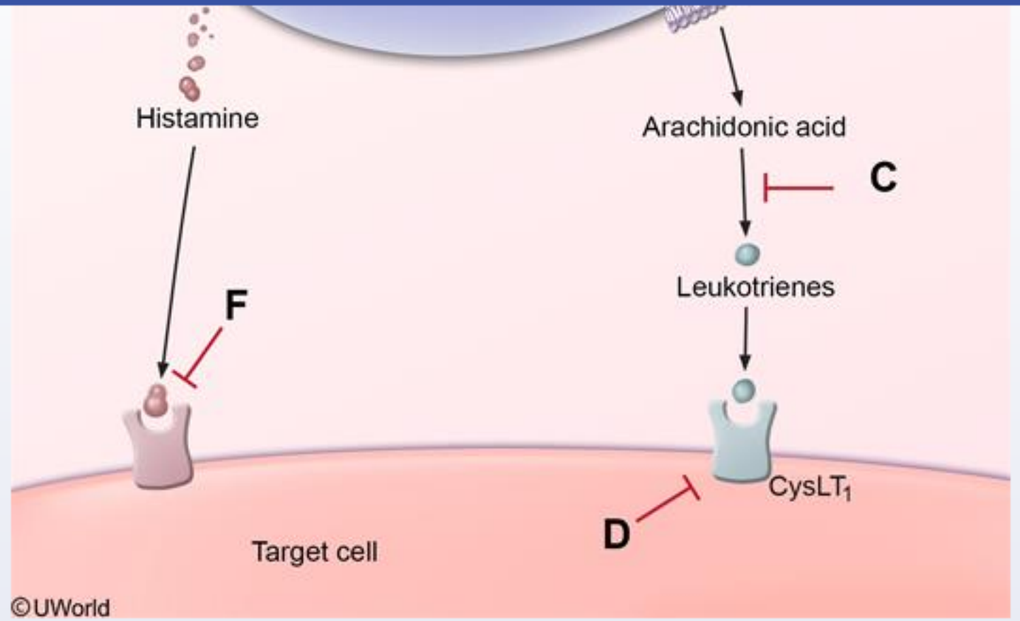
A. A
B. B
C. C
D. D
E. E



A. A
B. B
C. C
D. D
E. E
F. F

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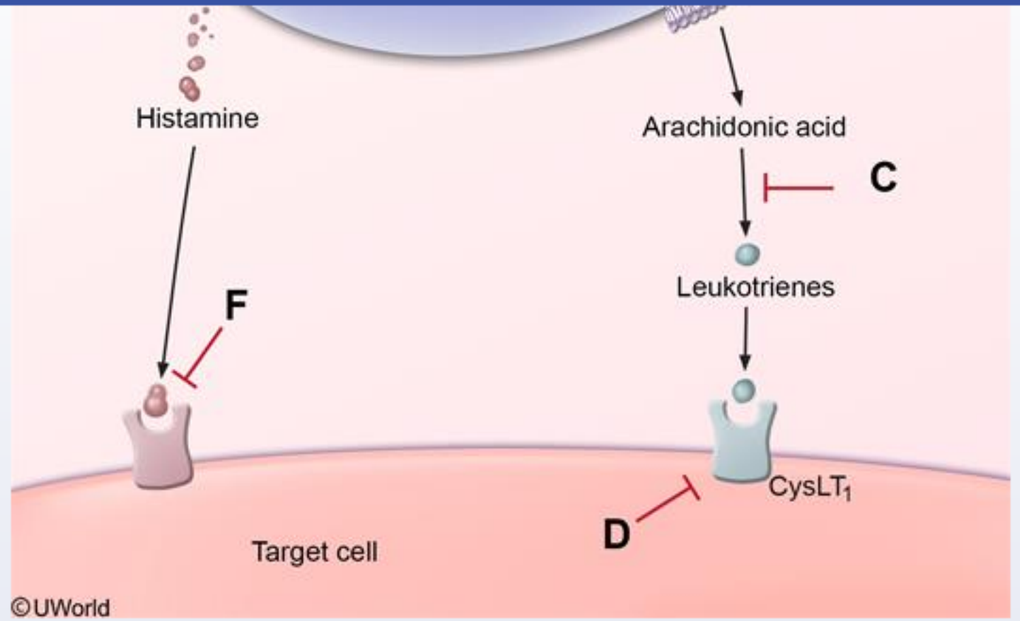


A. A (11%)
B. B (5%)
C. C (5%)
D. D (7%)
✓ E. E (65%)
F. F (4%)

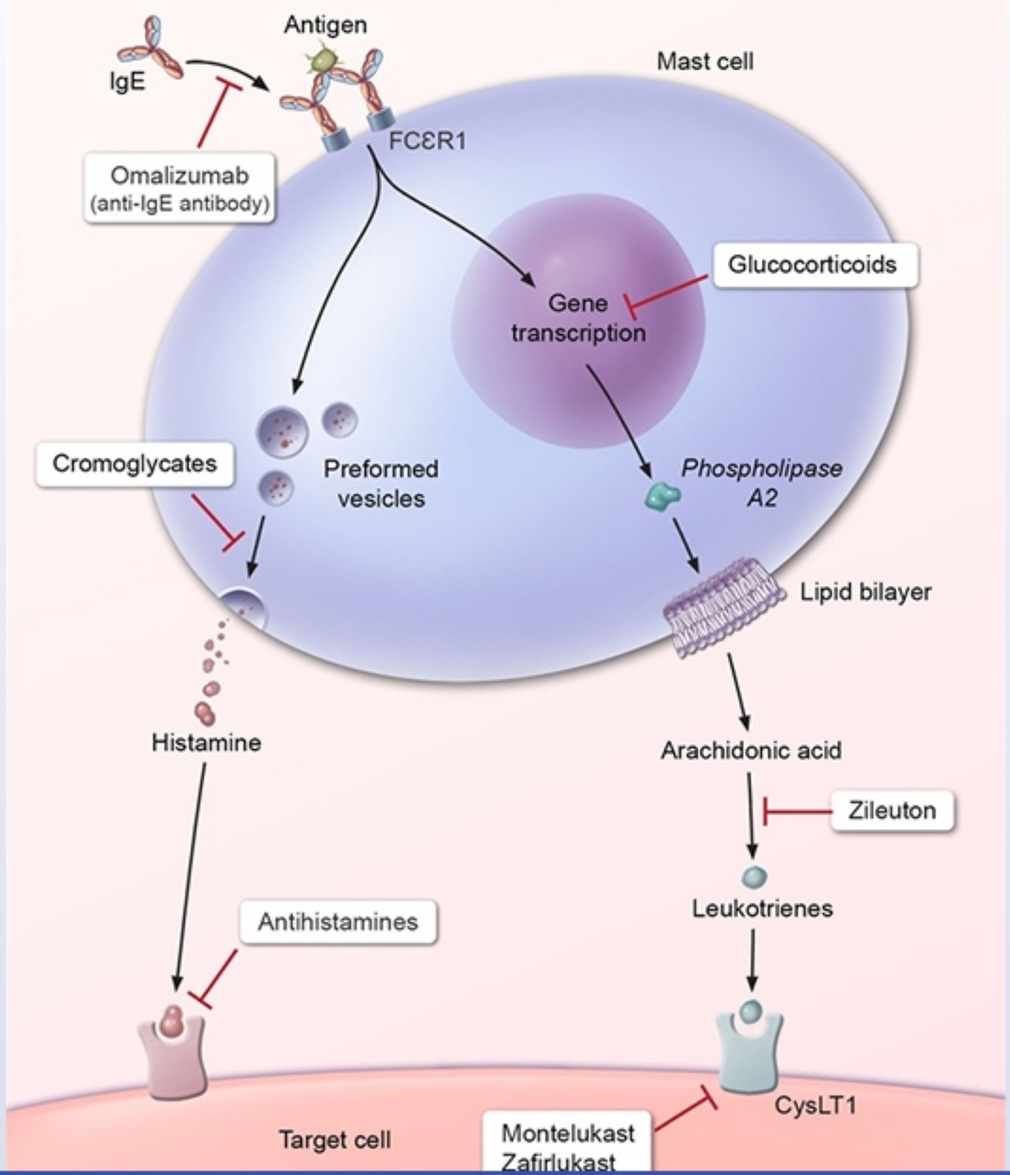
Omitted
Correct answer

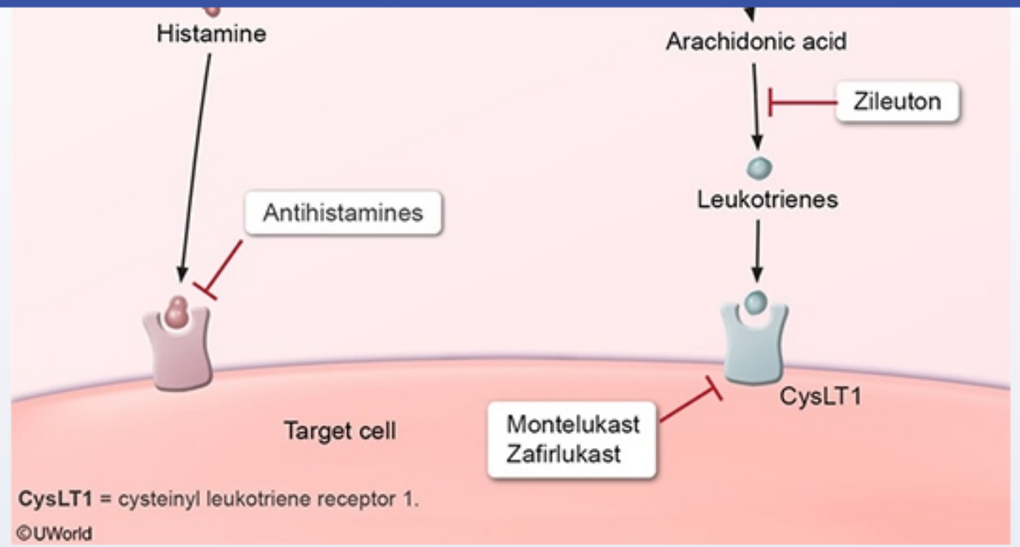
65%
Answered correctly

10 secs
Time Spent

01/10/2020
Last Updated

Mast cells & allergic response





Acute **bronchial constriction** during an asthma exacerbation begins with **mast cell activation** secondary to allergen interaction with IgE antibodies or nonimmune triggers (eg, exercise, cold exposure, chemical irritants). This results in the release of chemical mediators that cause immediate bronchial constriction, bronchial wall edema, and increased mucus production (early phase reaction). These mediators recruit additional inflammatory cells (eg, eosinophils, basophils, neutrophils, T lymphocytes) that lead to bronchial obstruction, which occurs several hours after the triggering event (late phase reaction).

Cromolyn and nedocromil **inhibit mast cell degranulation** and prevent release of preformed chemical mediators. These medications do not influence bronchial constriction directly; therefore, they are typically used to prevent acute attacks, rather than to treat acute exacerbations. Even though these drugs are less efficacious than inhaled glucocorticoids, they are very effective prophylactic agents for patients with seasonal symptoms, aspirin hypersensitivity, and exercise-induced asthma.

(Choice A) The anti-IgE antibody, omalizumab, inhibits IgE binding to mast cells, preventing mast cell degranulation. Omalizumab is used in some patients with severe, persistent asthma to lower IgE levels and reduce allergen-induced bronchial constriction.

(Choice B) Cleavage of membrane phospholipids by the enzyme phospholipase A2 leads to the formation of arachidonic acid, which is in turn converted into prostaglandins and leukotrienes. By inhibiting phospholipase A2 synthesis, glucocorticoids inhibit the release of these downstream mediators, decreasing airway hyperresponsiveness and inflammation.

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(Choice B) Cleavage of membrane phospholipids by the enzyme phospholipase A2 leads to the formation of arachidonic acid, which is in turn converted into prostaglandins and leukotrienes. By inhibiting phospholipase A2 synthesis, glucocorticoids inhibit the release of these downstream mediators, decreasing airway hyperresponsiveness and inflammation.

(Choices C and D) Zileuton is a selective inhibitor of the lipoxygenase pathway that leads to decreased formation of leukotrienes. Zafirlukast and montelukast are leukotriene receptor antagonists. These agents are typically used for chronic asthma prophylaxis.

(Choice F) Antihistamines are used to prevent and blunt an acute allergic response (as seen in allergic rhinitis) but have not been shown to improve bronchoconstriction in asthma.

Educational objective:
Cromolyn and nedocromil are mast cell-stabilizing agents that inhibit mast cell degranulation independent of the triggering stimulus. They are less effective than inhaled glucocorticoids and are considered second-line treatments for allergic rhinitis and bronchial asthma.

References

- The effects of anti-asthma drugs on mediator release from cultured human mast cells.
- Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction.

Pharmacology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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Cromolyn and nedocromil inhibit mast cell degranulation and prevent release of preformed chemical mediators. These medications do not

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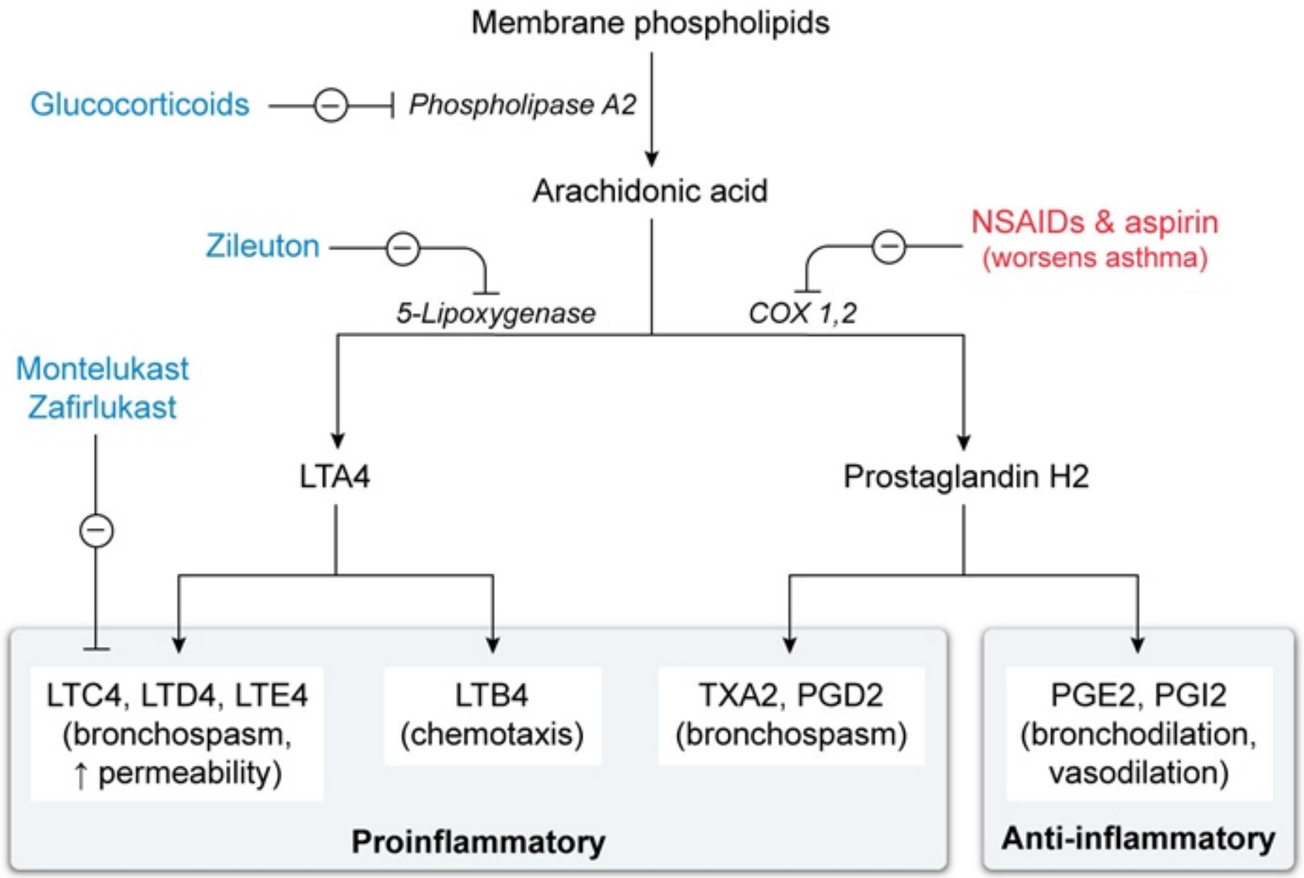
Arachidonic acid metabolic pathways in asthma



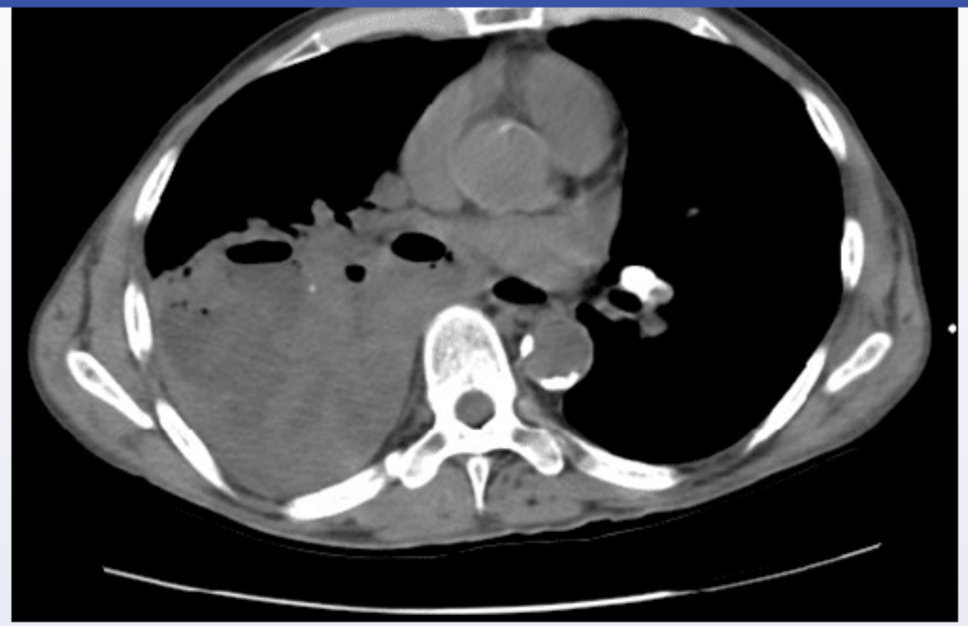
LT = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TX** = thromboxane.

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

A 41-year-old man comes to the emergency department due to 3 weeks of low-grade fever, productive cough, and a 4.5-kg (10-lb) weight loss. He drinks 12-18 beers a day. On physical examination, the patient appears cachectic. He has poor dentition and clubbing of the fingers. A foul-smelling sputum sample is expectorated and sent for Gram stain and culture. CT scan of the chest is shown below.

Which of the following antibiotics is the most appropriate treatment for this patient's condition?

- A. Cefazolin
- B. Ciprofloxacin
- C. Clindamycin
- D. Metronidazole



Which of the following antibiotics is the most appropriate treatment for this patient's condition?

- A. Cefazolin
- B. Ciprofloxacin
- C. Clindamycin
- D. Metronidazole
- E. Vancomycin

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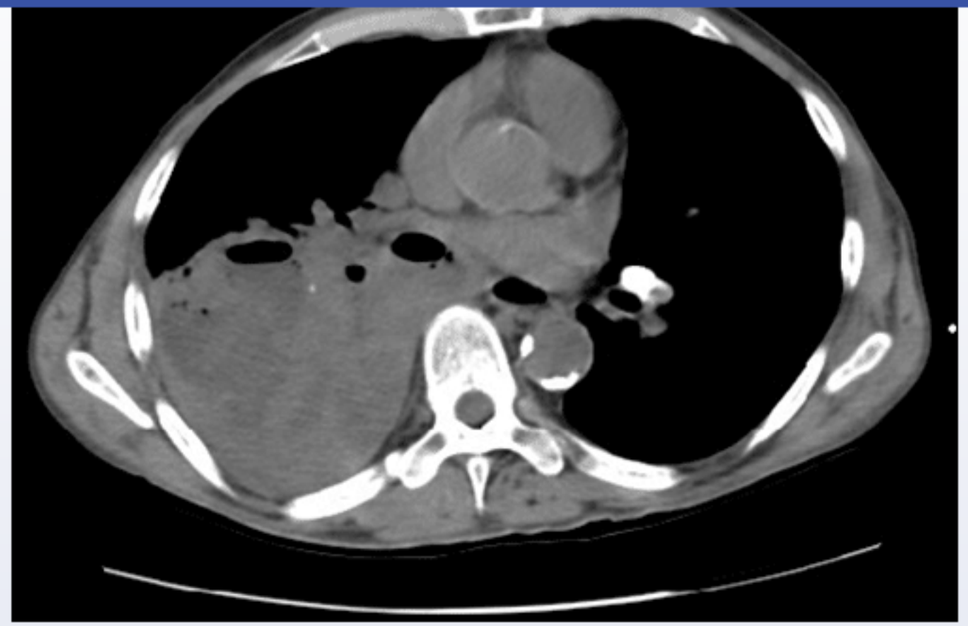

Which of the following antibiotics is the most appropriate treatment for this patient's condition?

- A. Cefazolin (11%)
- B. Ciprofloxacin (15%)
- ✓ C. Clindamycin (52%)
- D. Metronidazole (9%)
- E. Vancomycin (9%)

Omitted
Correct answer

52%
Answered correctly

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Time Spent

06/01/2020
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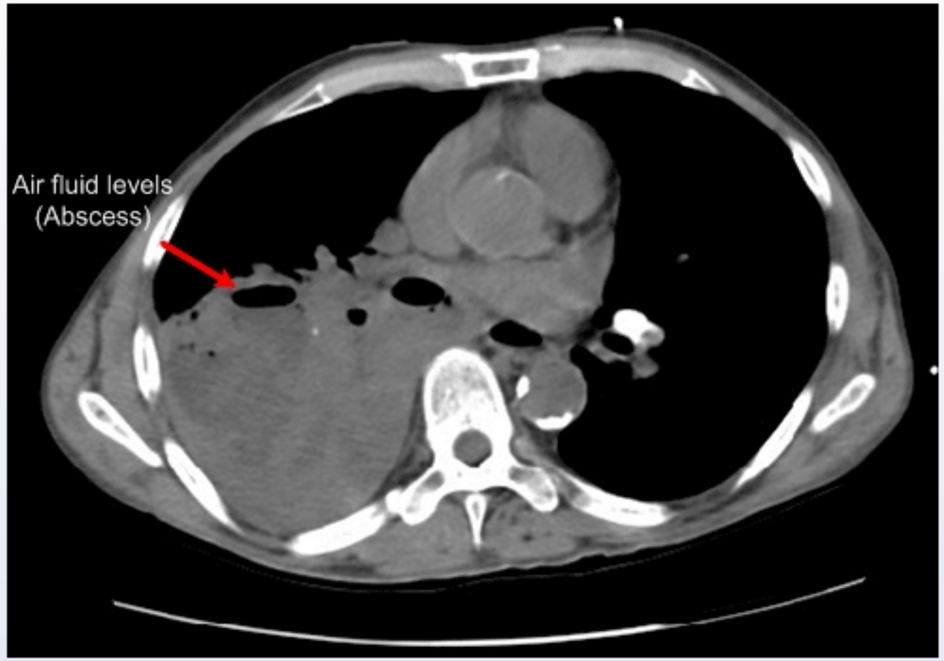

This patient's excessive alcohol consumption, subacute pulmonary symptoms, and dense lung opacity with an air-fluid level are consistent with a **lung abscess**. Most cases are due to the **aspiration of oropharyngeal flora** into the alveoli during reduced levels of consciousness from drug or **alcohol abuse** (which impairs cough and gag reflexes) or episodes of dysphagia (eg, previous stroke, esophageal stricture). Periodontal disease is frequently present, which increases the concentration of anaerobic bacteria in the gingival crevices. **Anaerobic oral organisms** such as *Bacteroides, Prevotella, Fusobacterium,* and *Peptostreptococcus* are the leading pathogens, but most lung abscesses are **polymicrobial** and tend to be composed of both anaerobic and aerobic organisms.

Manifestations typically include weeks or months of fever, cough with foul-smelling sputum, night sweats, and weight loss (digital clubbing also sometimes occurs). Diagnosis is usually made when chest imaging shows a dense fluid collection or cavitary infiltrate (often with an **air-fluid level**) in dependent portions of the lung (eg, superior portion of lower lobe). Treatment with oral **clindamycin** covers oral anaerobes and aerobic gram-positive organisms such as *Streptococcus pneumoniae*. Clindamycin binds to the bacterial 50S ribosomal subunit and disrupts bacterial protein synthesis (macrolides operate in a similar fashion).

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(Choices A and B) Although patients with alcoholism may develop monomicrobial *Klebsiella pneumoniae* lung abscesses, most lung abscesses are polymicrobial and contain anaerobes. Therefore, empiric treatment must include anaerobic coverage. Because cefazolin and ciprofloxacin do not possess anaerobic coverage, these antibiotics are not part of first-line therapy. Cefazolin has activity against a wide range of gram-positive and some gram-negative organisms. Ciprofloxacin has excellent activity against many gram-negative and some gram-positive organisms.

(Choice D) Metronidazole has excellent coverage against anaerobes but does not cover aerobic organisms. Adequate coverage against both aerobic organisms (eg, streptococci) and anaerobes is essential for successful treatment of lung abscesses.

(Choice E) Vancomycin targets the cell walls of gram-positive bacteria; it does not have efficacy against anaerobes or gram-negative bacteria. Therefore, vancomycin is not used as a primary treatment for lung abscess.

Educational objective:
Patients with alcoholism are at increased risk for lung abscess due to the aspiration of oral flora during periods of unconsciousness. Lung abscesses tend to be polymicrobial; they are usually composed of anaerobic oral flora (*Bacteroides, Prevotella, Fusobacterium,* and *Peptostreptococcus*) and aerobic bacteria. Clindamycin provides coverage against both anaerobic and aerobic organisms and has been traditionally used in the treatment of lung abscess.

References

- How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy.
- Etiology and outcome of community-acquired lung abscess.

Pharmacology	Pulmonary & Critical Care	Lung abscess
Subject	System	Topic

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A 36-year-old woman comes to the office due to dyspnea and weakness that are brought on while doing ordinary chores around the house. The patient has no other medical conditions and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her mother had similar symptoms and died at age 42. After an extensive workup, a lung biopsy is performed. Light microscopy of the tissue sample shows medial hypertrophy, intimal fibrosis, and decreased intraluminal diameter of the small branches of the pulmonary artery. Which of the following is the most appropriate pharmacotherapy for this patient's current condition?

A. Bosentan

B. Clopidogrel

C. Enalapril

D. Etanercept

E. Indomethacin

Submit

A 36-year-old woman comes to the office due to dyspnea and weakness that are brought on while doing ordinary chores around the house. The patient has no other medical conditions and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her mother had similar symptoms and died at age 42. After an extensive workup, a lung biopsy is performed. Light microscopy of the tissue sample shows medial hypertrophy, intimal fibrosis, and decreased intraluminal diameter of the small branches of the pulmonary artery. Which of the following is the most appropriate pharmacotherapy for this patient's current condition?

- ✓ A. Bosentan (74%)
- B. Clopidogrel (5%)
- C. Enalapril (6%)
- D. Etanercept (7%)
- E. Indomethacin (6%)

Omitted
Correct answer
A

74%
Answered correctly

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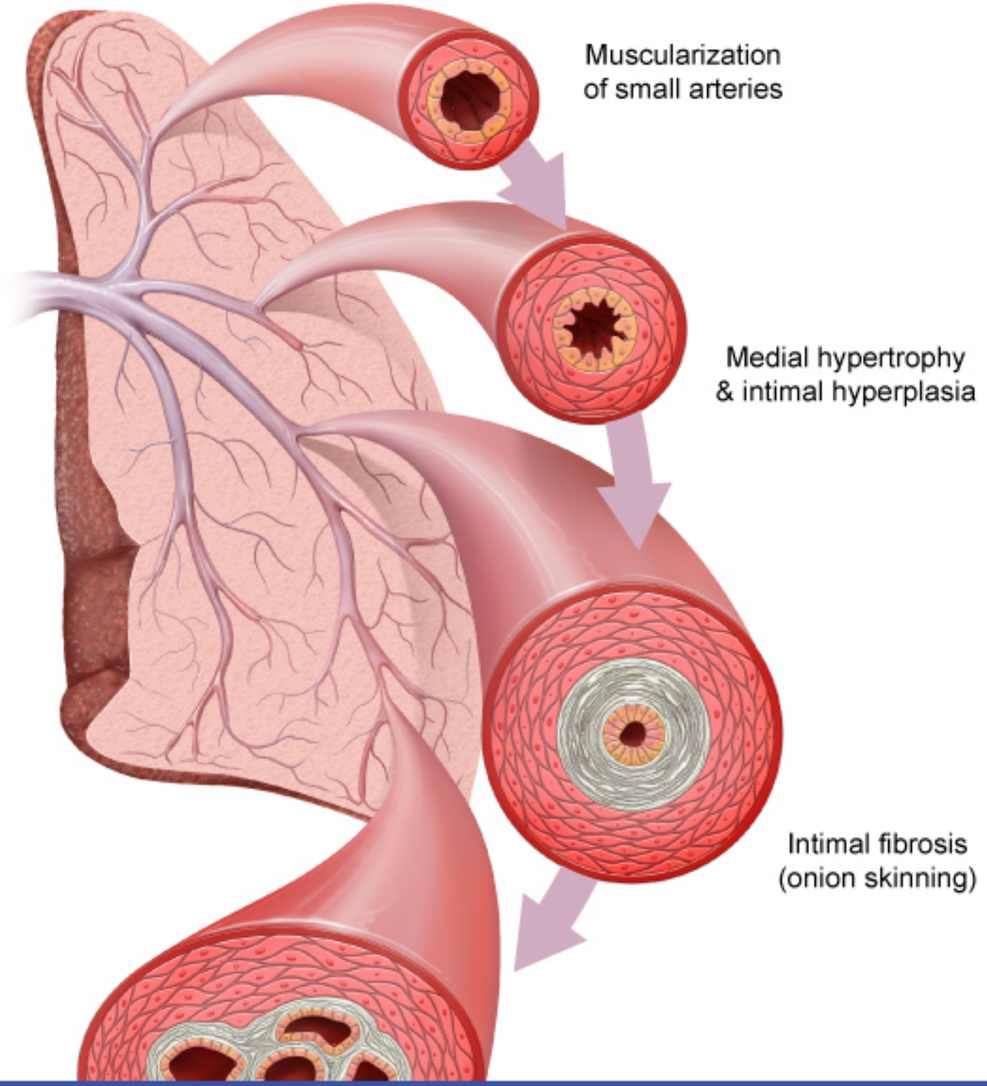
03/09/2020
Last Updated

Explanation

Pathogenesis of pulmonary arterial hypertension



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Pulmonary hypertension causes specific morphologic findings in the branches of the pulmonary arteries, including increased arteriolar smooth muscle thickness (**medial hypertrophy**), **intimal fibrosis**, and significant **luminal narrowing**. In the setting of severe hypertension, lesions can progress to form interlacing tufts of small vascular channels called **plexiform lesions**. These changes can occur in both pulmonary hypertension due to underlying cardiac, lung, or thrombotic disease and in pulmonary arterial hypertension (PAH).

PAH most commonly presents as dyspnea and exercise intolerance in women age 20-40. This patient's family history is suggestive of the familial form of PAH, which is most often caused by inactivating mutations involving the proapoptotic *BMPR2* gene. The resulting increase in endothelial and smooth muscle cell proliferation leads to vascular remodeling, elevated pulmonary vascular resistance, and progressively elevated pulmonary arterial pressure.

Although lung transplantation is the definitive treatment for PAH, medical therapy targeting the effects of endothelial dysfunction can help improve symptoms. **Bosentan** is an **endothelin-receptor antagonist** that blocks the effects of endothelin (a potent vasoconstrictor that also stimulates endothelial proliferation). Bosentan therapy decreases pulmonary arterial pressure and lessens the progression of vascular remodeling and right ventricular hypertrophy.

(Choice B) Clopidogrel inhibits ADP-induced platelet aggregation. It is used in atherosclerotic cardiovascular disease and to prevent acute stent thrombosis following percutaneous coronary intervention.

(Choice C) Enalapril is an angiotensin-converting enzyme inhibitor. It is used for the treatment of congestive heart failure, hypertension, and diabetic nephropathy.

(Choice D) Etanercept inhibits tumor-necrosis factor (TNF) activity by competitively binding to TNF and preventing it from interacting with cell surface receptors. It is an anti-inflammatory agent used for the treatment of rheumatoid arthritis, psoriasis, and psoriatic arthritis.

(Choice E) Indomethacin is a nonselective cyclooxygenase inhibitor that suppresses prostaglandin synthesis. It is used as an anti-inflammatory agent and pain reliever.

Educational objective:
Pulmonary arterial hypertension (PAH) typically affects young women and can be familial. It is characterized by luminal narrowing of the pulmonary arteries and arterioles, with medial hypertrophy, intimal fibrosis, and the eventual development of plexiform lesions. Bosentan is a competitive antagonist of endothelin receptors used for the treatment of PAH.

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Classification of pulmonary hypertension	
Pulmonary arterial hypertension (Group 1)	• Primary change in pulmonary arteries ◦ Hereditary (eg, *BMPR2* mutation) ◦ Connective tissue disease (eg, RA, SS) ◦ HIV infection • Treatment targeted at endothelial dysfunction
Pulmonary hypertension (Groups 2-5)	• Secondary to another disease process ◦ Left-sided heart failure ◦ Chronic lung disease/hypoxia ◦ Chronic pulmonary thromboembolism • Treatment aimed at underlying disease

RA = rheumatoid arthritis; SS = systemic sclerosis.

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Pharmacology	Pulmonary & Critical Care	Pulmonary Arterial Hypertension
Subject	System	Topic

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A 28-year-old man comes to the clinic due to cough and shortness of breath. The patient has a history of intermittent asthma controlled with an as-needed albuterol inhaler. Over the last month, he has noticed increased severity and frequency of his symptoms. The patient occasionally wakes up at night with coughing spells and has had to use his albuterol inhaler several times per week due to shortness of breath. An inhaled corticosteroid is prescribed to achieve better symptom control. In addition to an anti-inflammatory effect, which of the following effects also directly occurs as a result of this therapy?

A. Decreased production of lung surfactants

B. Decreased viscosity of bronchial mucus

C. Increased activity of phosphodiesterases

D. Increased quantity of surface-bound IgE

E. Increased responsiveness of beta-2 receptors

Submit

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A. Decreased production of lung surfactants (3%)

B. Decreased viscosity of bronchial mucus (24%)

C. Increased activity of phosphodiesterases (9%)

D. Increased quantity of surface-bound IgE (2%)

✓ E. Increased responsiveness of beta-2 receptors (60%)

Omitted
Correct answer
E

60%
Answered correctly

02 secs
Time Spent

04/07/2020
Last Updated

Explanation

Asthma is a complex disease involving both chronic inflammation and airway hyperreactivity. **Inhaled corticosteroids** (eg, fluticasone, budesonide) are a mainstay of asthma therapy. Corticosteroids reduce inflammation by inhibiting nuclear transcription of inflammatory genes (in part leading to downregulation of the enzyme phospholipase A2) to decrease the production of leukotrienes and other inflammatory mediators.

Although corticosteroids have no direct effect on bronchodilation, these drugs provide an additional benefit in asthma by **potentiating the bronchodilatory effect** of beta-2 agonists (eg, albuterol). This is accomplished by stimulating the **upregulation of beta-2 receptors** in

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Although corticosteroids have no direct effect on bronchodilation, these drugs provide an additional benefit in asthma by **potentiating the bronchodilatory effect** of beta-2 agonists (eg, albuterol). This is accomplished by stimulating the **upregulation of beta-2 receptors** in **bronchial smooth muscle**, increasing cellular responsiveness to adrenergic stimulus. This medication effect is similar to the permissive effect of endogenous cortisol on blood pressure, which involves upregulation of alpha-1 receptors and increased responsiveness of vascular smooth muscle cells to epinephrine.

(Choice A) Corticosteroids increase, rather than decrease, the production of lung surfactants and may be used to help prevent infant respiratory distress syndrome in premature infants.

(Choice B) Guaifenesin reduces the viscosity (ie, thickness) of respiratory tract mucus and is often used in the symptomatic management of viral upper respiratory tract infections. Decreased mucus viscosity is not a direct effect of corticosteroids.

(Choice C) Theophylline provides benefit in asthma by stimulating bronchodilation via inhibition of phosphodiesterase-3 and may also create an anti-inflammatory effect via inhibition of phosphodiesterase-4. Corticosteroids may somewhat decrease phosphodiesterase activity but likely do not have a significant effect.

(Choice D) Omalizumab is a monoclonal antibody that treats asthma by binding to free IgE to decrease IgE binding to surface receptors on mast cells and basophils. This inhibits the degranulation of inflammatory mediators. The anti-inflammatory effects of corticosteroids may also contribute to a decrease, rather than an increase, in surface-bound IgE.

Educational objective:
Corticosteroids (eg, fluticasone, budesonide) have multiple beneficial effects in the treatment of asthma. In addition to their anti-inflammatory effect, corticosteroids upregulate beta-2 receptors on bronchial smooth muscle to increase cellular responsiveness to adrenergic stimuli and potentiate the bronchodilatory response to inhaled beta-2 agonists (eg, albuterol).

References

- Glucocorticosteroids increase beta 2-adrenergic receptor transcription in human lung.

A pharmaceutical researcher is studying a new drug being developed for treatment of asthma that works by reversing irritant-induced bronchoconstriction. Laboratory guinea pigs are divided into 2 groups: a postvagotomy (complete transection of the vagus nerve) group and a normal study group. Both groups are exposed to irritants without receiving the study medication, and changes in bronchial diameters are recorded. Subsequently, both groups are exposed again to the irritants but are also given the study drug.

The study drug is most likely similar to which of the following medications?

A. Albuterol
B. Flunisolide
C. Ipratropium
D. Nifedipine
E. Theophylline
F. Zileuton

Submit

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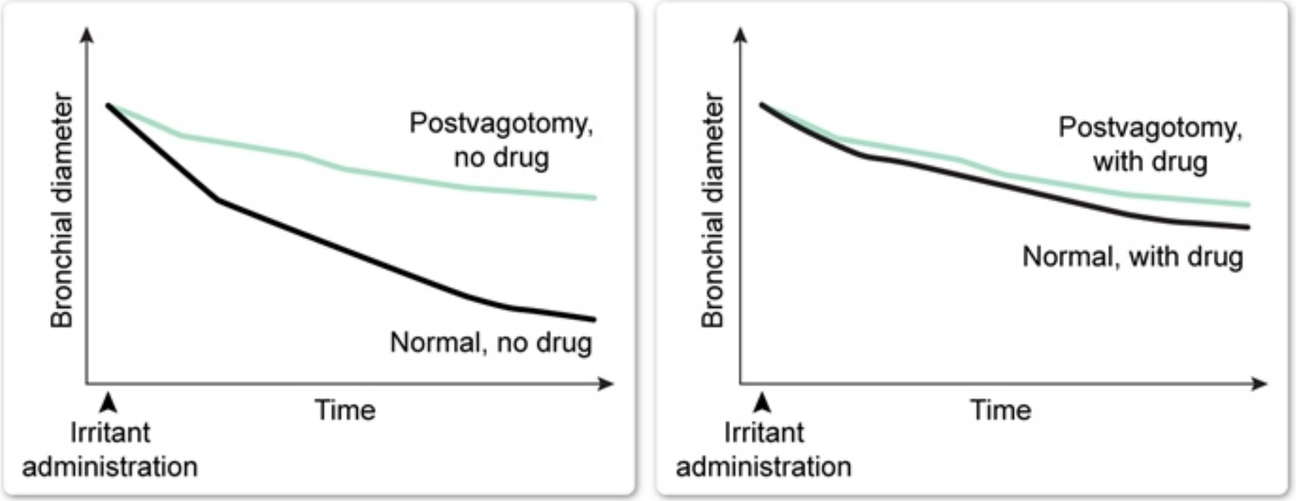

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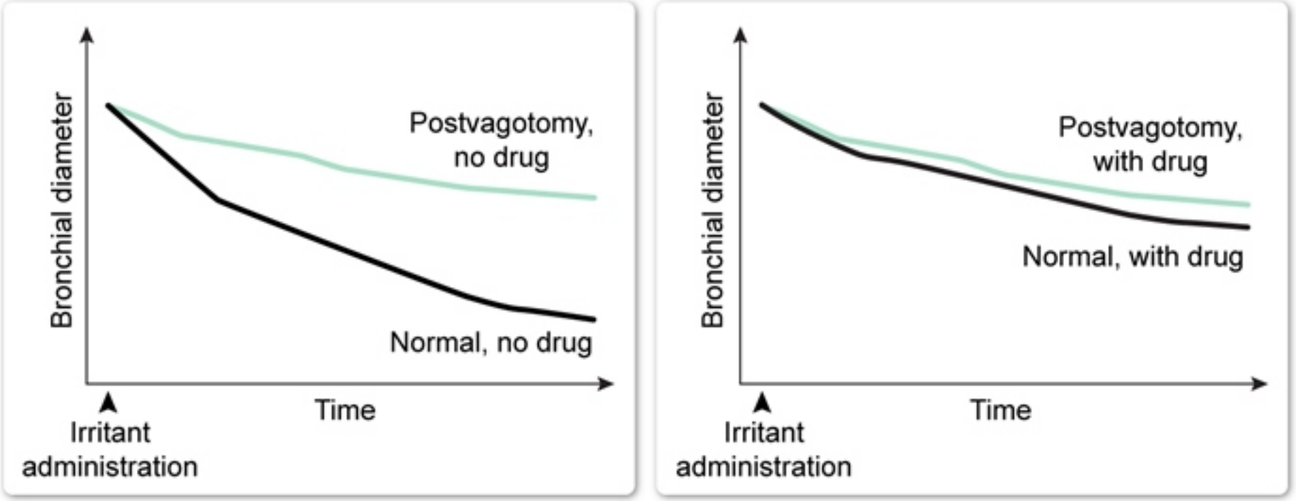

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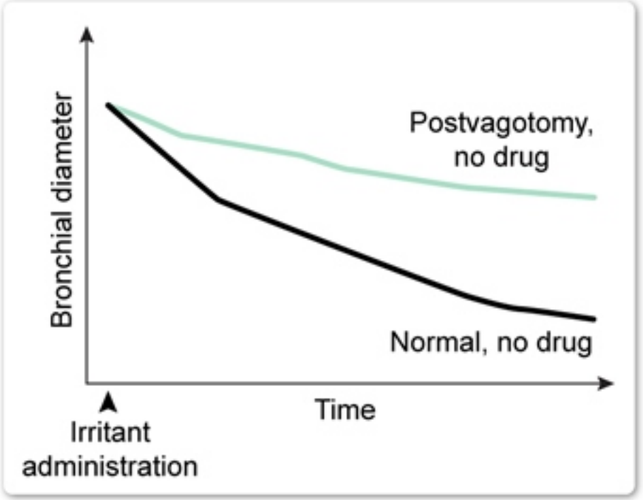

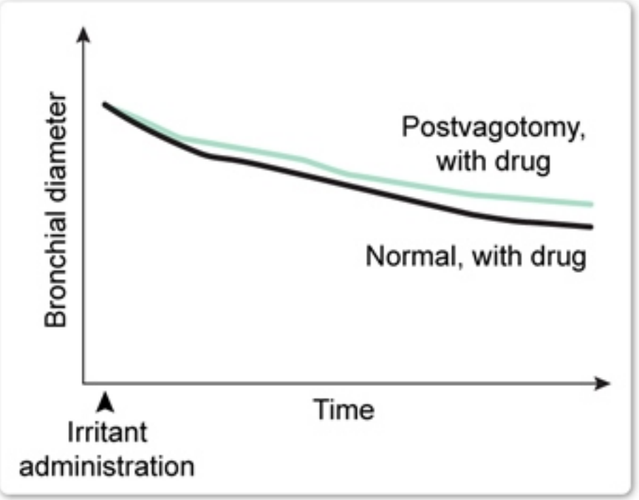

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- F. Zileuton

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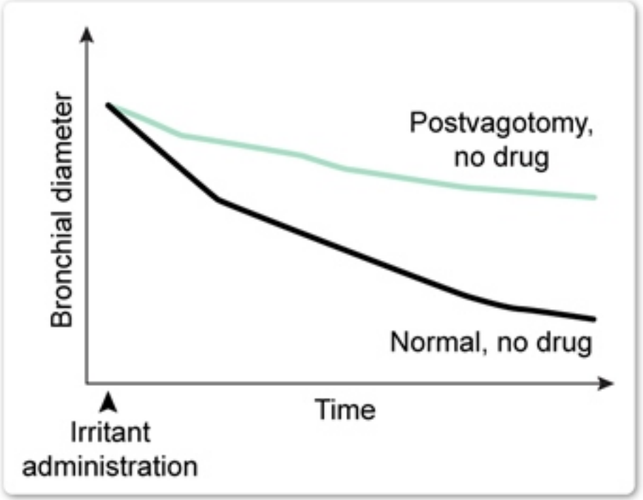

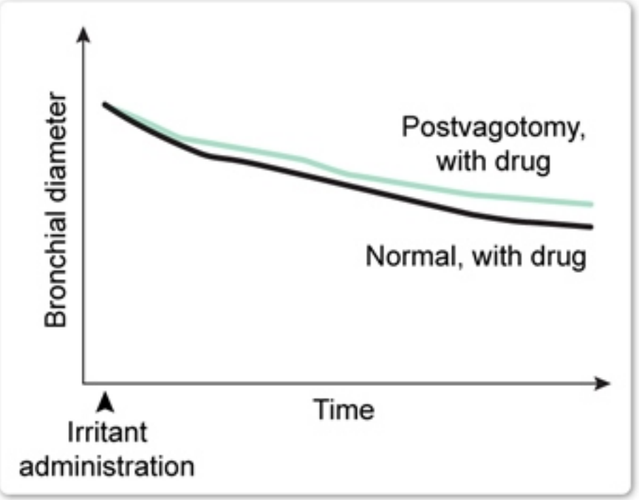

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The study drug is most likely similar to which of the following medications?

- A. Albuterol (30%)
- B. Flunisolide (1%)
- ✓ C. Ipratropium (55%)
- D. Nifedipine (1%)
- E. Theophylline (7%)
- F. Zileuton (4%)

Omitted
Correct answer

55%
Answered correctly

07 secs
Time Spent

01/10/2020
Last Updated

The figure on the left shows a decrease in bronchial diameter of normal lungs following administration of an irritant but minimal change in bronchial diameter of lungs without an intact vagus nerve. This implies that the bronchoconstriction is mediated by the **parasympathetic** nervous system. When the vagus nerve is stimulated (eg, via an inhaled irritant), **acetylcholine** is released and produces **bronchoconstriction** by acting on muscarinic receptors. The figure on the right demonstrates minimal decrease in bronchial diameter in normal lungs following administration of the irritant, suggesting that the study medication blocks the action of acetylcholine. **Ipratropium**, an anticholinergic and derivative of atropine, has this effect.

Ipratropium and other anticholinergic drugs used for **obstructive lung disease** (eg, tiotropium) are less potent bronchodilators than beta-2 adrenergic agonists but can enhance the bronchodilatory effect of these agents. In addition, ipratropium and similar drugs block the parasympathetic stimulation of tracheobronchial submucosal glands, decreasing mucus secretion and providing further benefit in treating asthma and chronic obstructive pulmonary disease (COPD).

(Choice A) Albuterol is a short-acting selective beta-2 adrenergic agonist that is the first-line treatment for asthma and COPD. The bronchodilatory effects of albuterol are independent of parasympathetic innervation.

(Choice B) Inhaled glucocorticoids (eg, flunisolide) have potent local anti-inflammatory effects in the airway and are used in the treatment of persistent asthma and COPD with frequent exacerbations.

(Choice D) Nifedipine causes bronchodilation by blocking calcium influx into bronchial smooth muscle cells; however, the drug is generally not used in treating obstructive lung disease.

(Choice E) Methylxanthines, such as theophylline and aminophylline, cause bronchodilation by blocking phosphodiesterase activity, thereby increasing the intracellular concentration of cyclic AMP.

(Choice F) Zileuton inhibits 5-lipoxygenase and thereby decreases the production of leukotrienes to reduce bronchoconstriction and improve asthma symptoms.

Educational objective:
Ipratropium, an anticholinergic agent and derivative of atropine, treats obstructive lung disease by blocking acetylcholine at muscarinic receptors, which prevents bronchoconstriction and reduces mucus secretion from tracheobronchial submucosal glands.

References

parasympathetic stimulation of tracheobronchial submucosal glands, decreasing mucus secretion and providing further benefit in treating asthma and chronic obstructive pulmonary disease (COPD).

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References

- Muscarinic receptor antagonists: effects on pulmonary function.
- The pharmacological rationale for combining muscarinic receptor antagonists and ß-adrenoceptor agonists in the treatment of airway and bladder disease.

Pharmacology	Pulmonary & Critical Care	COPD
Subject	System	Topic

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A 21-year-old man with asthma comes to the office for follow-up. His asthma symptoms are not adequately controlled with albuterol as needed, and a daily inhaled therapy was added at the previous visit. The patient says he feels much better and has been using his rescue inhaler less frequently. He has no other medical conditions. The patient does not use tobacco or illicit drugs and drinks 1 or 2 12-oz cans of beer daily. He received childhood vaccinations but has refused the flu and pneumococcal vaccines. Vital signs are within normal limits, and lungs are clear to auscultation. White mucosal plaques that can be easily scraped off using a tongue depressor are present in the oropharynx. The remainder of the physical examination shows no abnormalities. Which of the following measures would have been most effective in preventing this patient's current abnormal findings?

- A. Avoiding alcohol intake
- B. Obtaining recommended vaccines
- C. Oral rinsing after inhaler use
- D. Periodic glucose monitoring
- E. Taking prophylactic antibiotics
- F. Using vitamin supplements

Submit

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- A. Avoiding alcohol intake (1%)
- B. Obtaining recommended vaccines (1%)
- ✓ C. Oral rinsing after inhaler use (94%)
- D. Periodic glucose monitoring (0%)
- E. Taking prophylactic antibiotics (1%)
- F. Using vitamin supplements (0%)

Omitted
Correct answer
C

94%
Answered correctly

02 secs
Time Spent

06/25/2020
Last Updated

Explanation

Patients with intermittent **asthma** may be managed with an as-needed, short-acting beta-agonist alone; however, persistent symptoms or severe disease necessitates the addition of long-term controller medications. **Inhaled glucocorticoids** are recommended for all such patients and have

Explanation

Patients with intermittent **asthma** may be managed with an as-needed, short-acting beta-agonist alone; however, persistent symptoms or severe disease necessitates the addition of long-term controller medications. **Inhaled glucocorticoids** are recommended for all such patients and have been shown to improve symptoms, reduce the need for short-acting bronchodilators, and lower the risk of serious exacerbations and associated hospitalization.

Low-dose inhaled glucocorticoids are well tolerated and rarely cause systemic adverse effects. However, poor inhalation technique can cause much of the medication to deposit on the oral mucous membranes, where it is ineffective and can lead to **oropharyngeal candidiasis** (OPC) (evidenced by white plaques that are easily scraped off). Patients can avoid this complication by using a spacer and **rinsing the mouth** after inhalation. Dysphonia unrelated to OPC can also occur with inhaled glucocorticoids due to myopathy of laryngeal muscles and mucosal irritation.

(Choice A) Excessive alcohol intake may increase the risk of developing OPC; however, this patient's intake of 1 or 2 beers per day is within acceptable limits and is an unlikely contributing factor.

(Choice B) Diphtheria (due to *Corynebacterium diphtheriae*) is a serious infection that typically presents with pharyngitis and gray oropharyngeal pseudomembranes; it can be prevented with vaccination. However, there is no vaccine to prevent OPC.

(Choice D) Patients with chronically elevated blood glucose levels have increased risk of developing OPC; however, there is no evidence that this patient has poorly controlled diabetes mellitus.

(Choice E) Prophylactic antibiotics are not indicated for OPC and, in fact, are likely to increase the risk of developing OPC by altering the normal oropharyngeal bacterial flora. Prophylactic antifungals are also not indicated for OPC.

(Choice F) Vitamin A deficiency can impair cell-mediated immunity and create higher susceptibility to OPC. However, patients with vitamin A deficiency typically have drying and thickening of the skin and ocular conjunctivae. Improper administration of inhaled glucocorticoids is far more likely in this patient.

Educational objective:
Improper administration of inhaled glucocorticoids for the treatment of asthma can lead to adverse effects, including oropharyngeal candidiasis and dysphonia. Using a spacer during administration and rinsing the mouth after each use can help prevent these adverse effects.

References

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References

- Influence of mouth washing procedures on the removal of drug residues following inhalation of corticosteroids.

Pharmacology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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Pharmacology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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An 18-year-old woman comes to the clinic due to intermittent dry cough, wheezing, and shortness of breath. She recently began practicing twice a day for her college track team and has been experiencing these symptoms with running. Her symptoms have been limiting her ability to complete practice but usually resolve after several minutes of rest. Medical history includes childhood asthma that has not required treatment for the past 5 years. The patient is prescribed a medication that reduces bronchoconstriction by inhibiting the interaction of inflammatory mediators with cell surface receptors. Which of the following drugs was most likely used in this patient?

A. Albuterol
B. Dextromethorphan
C. Fluticasone
D. Ipratropium
E. Montelukast
F. Zileuton

Submit

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A. Albuterol (3%)
B. Dextromethorphan (0%)
C. Fluticasone (9%)
D. Ipratropium (2%)
✓ E. Montelukast (75%)
F. Zileuton (9%)

Omitted
Correct answer
E

75%
Answered correctly

02 secs
Time Spent

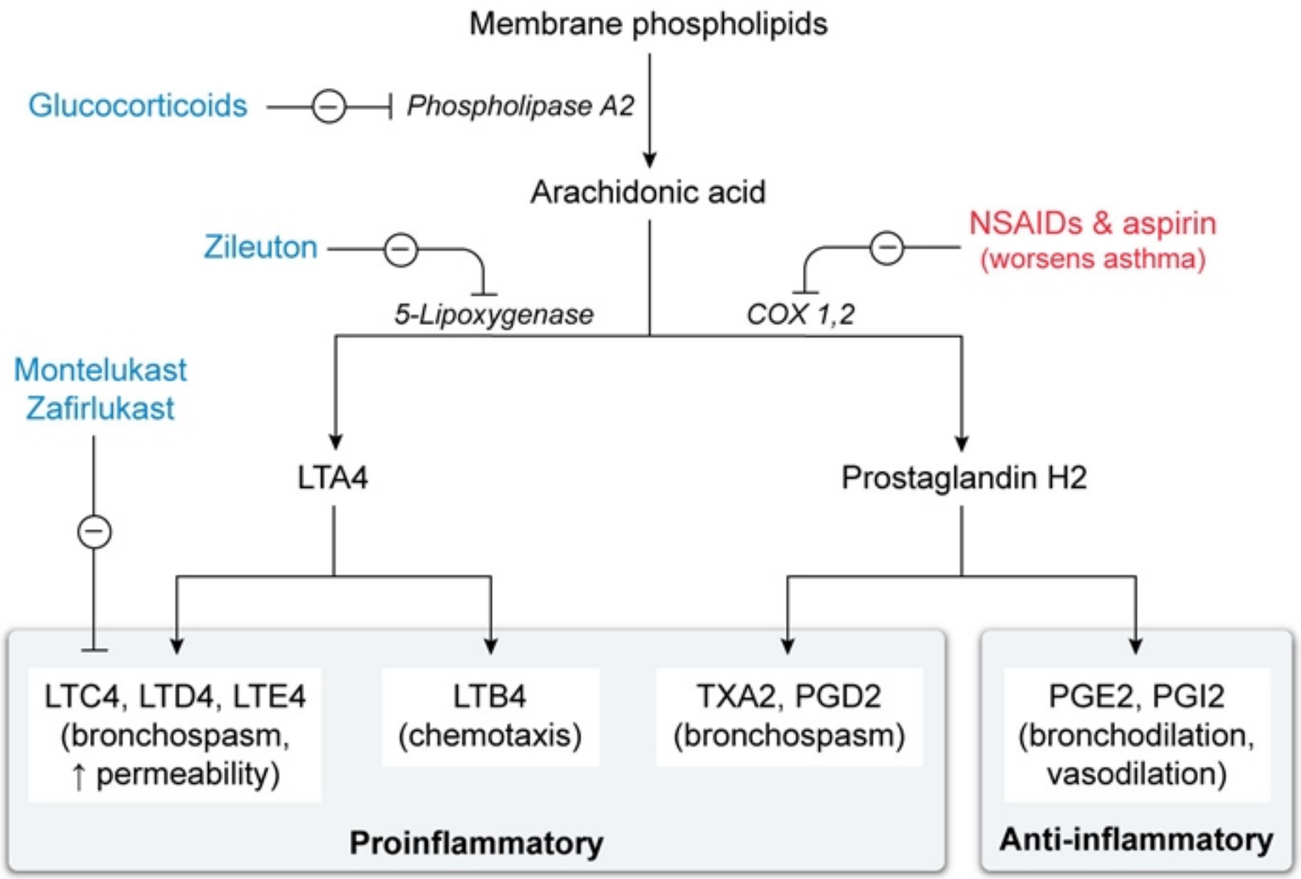
04/15/2020
Last Updated

Explanation

Arachidonic acid metabolic pathways in asthma

Membrane phospholipids

Arachidonic acid metabolic pathways in asthma



LT = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TX** = thromboxane.

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Exercise-induced bronchoconstriction is common in patients with underlying **asthma**. Asthma occurs due to a complex inflammatory response to the environment that involves Th2 lymphocytes, eosinophils, and mast cells. Eosinophils and mast cells synthesize and release **leukotrienes**, which are inflammatory mediators that induce bronchial smooth muscle contraction **(bronchoconstriction)**, bronchial **mucus secretion**, and

Exercise-induced bronchoconstriction is common in patients with underlying **asthma**. Asthma occurs due to a complex inflammatory response to the environment that involves Th2 lymphocytes, eosinophils, and mast cells. Eosinophils and mast cells synthesize and release **leukotrienes**, which are inflammatory mediators that induce bronchial smooth muscle contraction **(bronchoconstriction)**, bronchial **mucus secretion**, and bronchial **edema**. The leukotrienes mainly responsible for these responses are the cysteinyl-containing leukotrienes such as leukotriene C4, D4, and E4.

Leukotriene receptor antagonists (eg, montelukast, zafirlukast) effectively treat asthma by binding to leukotriene receptors on bronchial smooth muscle cells and blocking the effects of cysteinyl-containing leukotrienes.

(Choice A) Albuterol causes short-acting bronchodilation via selective stimulation of beta 2 receptors. It is typically used as an as-needed rescue inhaler in patients with asthma.

(Choice B) Dextromethorphan suppresses cough via stimulation of sigma opioid receptors in the CNS (it does not stimulate mu or delta opioid receptors and therefore does not cause other typical opioid effects). It is commonly used in cold medication but is not effective for treatment of asthma.

(Choice C) Inhaled corticosteroids (eg, fluticasone, budesonide) help treat asthma by inhibiting nuclear transcription of inflammatory genes leading to widespread anti-inflammatory effects. One effect is reduced activity of the enzyme phospholipase A2 to decrease the production of leukotrienes. Corticosteroids do not block cell surface receptors.

(Choice D) Ipratropium stimulates bronchodilation via blockade of the binding of acetylcholine (a neurotransmitter) to muscarinic receptors. Inhaled ipratropium is sometimes used in the treatment of asthma but is more commonly used for chronic obstructive pulmonary disease.

(Choice F) Zileuton is a 5-lipoxygenase enzyme inhibitor that reduces the production of leukotrienes (it does not block leukotriene cell surface receptors). It can be used for treatment of asthma, but it is often avoided due to concerns about toxicity.

Educational objective:
The cysteinyl-containing leukotrienes (ie, leukotriene C4, D4, and E4) are inflammatory mediators that stimulate bronchoconstriction, bronchial mucus secretion, and bronchial edema to contribute to the pathogenesis of asthma. Leukotriene receptor antagonists (eg, montelukast, zafirlukast) treat asthma by binding to leukotriene receptors on bronchial smooth muscle cells and blocking these effects.

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Pharmacology	Pulmonary & Critical Care	Leukotriene receptor antagonists
Subject	System	Topic

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A 43-year-old man comes to the office due to occasional dyspnea that awakens him at night. This symptom started approximately a year ago after a severe upper respiratory tract infection, and since then he has also had an episodic cough. The patient has no other medical problems and takes no medications. He has no drug allergies and does not use tobacco, alcohol, or illicit drugs. His older brother has atopic dermatitis. Vital signs are normal. Lung auscultation reveals bilateral normal breath sounds with no wheezing or crackles. Heart sounds are normal, and there is no extremity edema. Pulmonary function tests are as follows:

FEV1	88% of predicted
FEV1/FVC	84%
Diffusion capacity for carbon monoxide	95% of predicted

Administration of which of the following medications would be most useful during further diagnostic evaluation of this patient?

- A. Epinephrine
- B. Gadolinium
- C. Ipratropium bromide
- D. Levalbuterol
- E. Methacholine
- F. Regadenoson
- G. Theophylline

Submit

A 43-year-old man comes to the office due to occasional dyspnea that awakens him at night. This symptom started approximately a year ago after a severe upper respiratory tract infection, and since then he has also had an episodic cough. The patient has no other medical problems and takes no medications. He has no drug allergies and does not use tobacco, alcohol, or illicit drugs. His older brother has atopic dermatitis. Vital signs are normal. Lung auscultation reveals bilateral normal breath sounds with no wheezing or crackles. Heart sounds are normal, and there is no extremity edema. Pulmonary function tests are as follows:

FEV1	88% of predicted
FEV1/FVC	84%
Diffusion capacity for carbon monoxide	95% of predicted

Administration of which of the following medications would be most useful during further diagnostic evaluation of this patient?

A. Epinephrine (0%)
B. Gadolinium (1%)
C. Ipratropium bromide (3%)
D. Levalbuterol (3%)
✓ E. Methacholine (89%)
F. Regadenoson (0%)
G. Theophylline (1%)

Omitted
Correct answer
E

89%
Answered correctly

02 secs
Time Spent

05/18/2020
Last Updated

This patient's intermittent nocturnal dyspnea and episodic cough that began after a respiratory infection suggest a diagnosis of **asthma**, a disease characterized by airway inflammation and bronchial hyperreactivity to various stimuli, including physical, chemical, and allergenic irritants. Patients often have a family history of other diseases in the "allergic triad" (ie, allergic rhinitis, atopic dermatitis, asthma). Asthma is an obstructive airway disease (FEV1/FVC ≤70%); however, **airflow obstruction is variable**, and lung function studies may be normal between exacerbations.

Bronchoprovocation testing can be useful in diagnosis when a patient presents with a history concerning for asthma but has normal spirometry values. Methacholine is an inhaled muscarinic cholinergic agonist that induces bronchoconstriction; patients are given increasing doses followed by serial spirometry. Patients with asthma demonstrate **hyperresponsivity** to bronchoprovocation with a reduction in FEV1 at lower doses than in those without asthma.

Conversely, bronchodilator administration can help diagnose patients who have obstructive values on spirometry at baseline. Spirometry is performed before and after administration of a bronchodilator (eg, levalbuterol); reversal of the airflow obstruction after therapy suggests the diagnosis of asthma, while irreversible obstruction suggests an alternative diagnosis (eg, bronchiolitis, COPD). However, in a patient who is currently asymptomatic with normal lung function studies, this is unlikely to aid in diagnosis **(Choice D)**.

(Choice A) Epinephrine, an adrenergic agonist, is used for treatment of anaphylaxis. Patients can develop respiratory compromise due to swelling of the airways; however, this is typically accompanied by hypotension and skin involvement (eg, hives, lip swelling). Epinephrine is not indicated in the workup of asthma.

(Choices B and F) Gadolinium is a contrast material used for MRI. Regadenoson is a coronary vasodilator used in cardiac stress testing to evaluate for coronary artery disease. Neither is indicated in the workup of asthma.

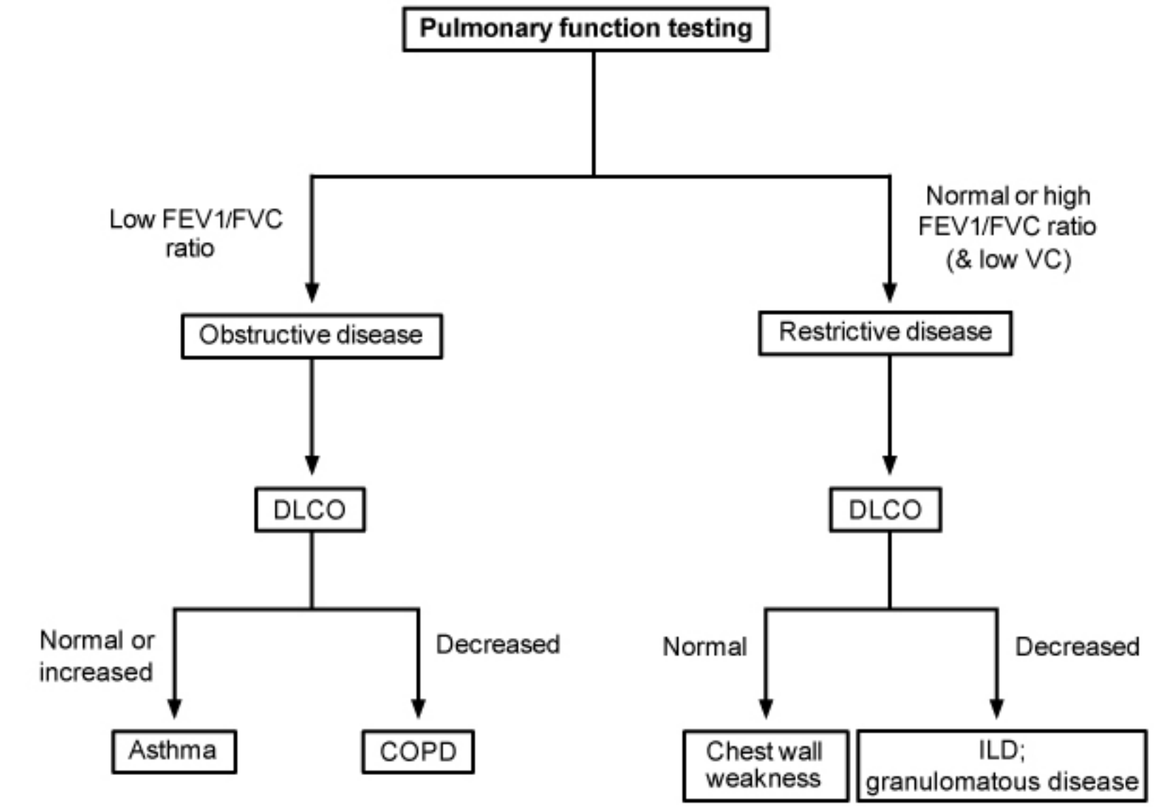
(Choices C and G) Ipratropium bromide is a muscarinic cholinergic antagonist used for asthma and chronic obstructive pulmonary disease, and theophylline is a phosphodiesterase-3 inhibitor sometimes used for refractory asthma. These medications can treat asthma but are not used for diagnostic purposes.

Educational objective:
Asthma is characterized by reversible airway obstruction, and lung function tests may be normal between exacerbations. Bronchoprovocation can be used to aid diagnosis in patients with normal spirometry; methacholine is administered and followed by serial spirometry. Patients with asthma demonstrate hyperresponsivity to the stimulus, leading to FEV1 reductions at lower doses than in those without asthma.

References

This patient's intermittent nocturnal dyspnea and episodic cough that began after a respiratory infection suggest a diagnosis of **asthma**, a disease

Exhibit Display



COPD = chronic obstructive pulmonary disease; **DLCO** = diffusion capacity of the lung for carbon monoxide; **FEV1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **ILD** = interstitial lung disease; **VC** = vital capacity.

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Exhibit Display

Normal lung function study values	
FEV1/FVC	~80%
FEV1	≥80% of predicted value
DLCO	≥80%-120% of predicted value

DLCO = diffusion capacity for carbon monoxide.

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Asthma is characterized by reversible airway obstruction, and lung function tests may be normal between exacerbations. Bronchoprovocation can be used to aid diagnosis in patients with normal spirometry; methacholine is administered and followed by serial spirometry. Patients with asthma demonstrate hyperresponsivity to the stimulus, leading to FEV1 reductions at lower doses than in those without asthma.

References

- A stepwise approach to the interpretation of pulmonary function tests.

Pharmacology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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A 24-year-old woman, gravida 1 para 0, at 14 weeks gestation, comes to the emergency department due to left leg swelling and pain for the past 2 days. She has had no chest pain or shortness of breath. The patient has no prior medical conditions and her only medication is a prenatal vitamin. She is a lifetime nonsmoker. Physical examination shows 1+ edema of the left lower extremity to the knee, associated with mild erythema. The left calf diameter measures 3 cm greater than the right. Doppler ultrasonography shows left popliteal and femoral vein thrombosis. Serum creatinine level is 0.7 mg/dL. Which of the following is the most appropriate pharmacotherapy for this patient?

- A. Apixaban
- B. Clopidogrel
- C. Dabigatran
- D. Enoxaparin
- E. Low-dose aspirin
- F. Tissue plasminogen activator
- G. Warfarin

Submit

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- A. Apixaban (3%)
- B. Clopidogrel (4%)
- C. Dabigatran (4%)
- ✓ D. Enoxaparin (64%)
- E. Low-dose aspirin (3%)
- F. Tissue plasminogen activator (15%)
- G. Warfarin (3%)

Omitted
Correct answer
D

64%
Answered correctly

01 sec
Time Spent

05/03/2020
Last Updated

Explanation

Pregnancy increases the risk of **venous thromboembolism** (VTE) due to anatomic changes (eg, uterine compression of the inferior vena cava and iliac veins) and physiologic hypercoagulability (eg, increased production of clotting factors, decreased protein S levels, protein C resistance).

Pregnancy increases the risk of **venous thromboembolism** (VTE) due to anatomic changes (eg, uterine compression of the inferior vena cava and iliac veins) and physiologic hypercoagulability (eg, increased production of clotting factors, decreased protein S levels, protein C resistance). **Heparins** are ideal anticoagulants for most pregnant women as they do not cross the placenta and the risk of fetal bleeding and teratogenicity is low:

- **Low-molecular-weight heparin (LMWH)** (eg, enoxaparin, dalteparin) is preferred as it has a relatively long half-life (4.5 hours) and does not require routine laboratory monitoring. However, it is renally cleared and cannot be used in patients with severe renal insufficiency (creatinine clearance <30 mL/min).
- Unfractionated heparin has a short half-life (1-2 hours) and requires frequent lab draws (ie, PTT) due to its more varied anticoagulant effect. However, it may be used in patients with renal insufficiency. It is also used in place of LMWH at term (37 weeks gestation) as it can be discontinued at the onset of labor to minimize hemorrhagic risk.

(Choices A and C) Direct thrombin inhibitors (eg, dabigatran) and factor Xa inhibitors (eg, apixaban) are not recommended in pregnant women. Both have been associated with fetal toxicity in animal studies.

(Choices B and E) Clopidogrel and aspirin have no role in acute VTE treatment. Clopidogrel, which blocks the platelet adenosine diphosphate receptor and limits platelet aggregation, is used in treatment of coronary artery disease, acute coronary syndrome, and prevention of recurrent ischemic stroke. Low-dose aspirin is prescribed to certain pregnant patients at risk of preeclampsia.

(Choice F) Recombinant tissue plasminogen activator is used for clot lysis. It has a high risk of major bleeding and is typically reserved for those with massive deep vein thrombosis at risk of limb ischemia or life-threatening pulmonary embolism with hypotension. Anticoagulation alone is preferred for VTE in hemodynamically stable patients.

(Choice G) Warfarin crosses the placenta, increasing risks of teratogenicity and fetal hemorrhage, and is typically avoided in pregnancy.

Educational objective:
Heparins are ideal anticoagulants for most patients with thromboembolic disease in pregnancy as they do not cross the placenta and therefore the risk of fetal bleeding or teratogenicity is low. Low molecular weight heparin (eg, enoxaparin) is the preferred therapy, with patients transitioned to unfractionated heparin at term.

- Unfractionated heparin has a short half-life (1-2 hours) and requires frequent lab draws (ie, PTT) due to its more varied anticoagulant effect. However, it may be used in patients with renal insufficiency. It is also used in place of LMWH at term (37 weeks gestation) as it can be discontinued at the onset of labor to minimize hemorrhagic risk.

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Heparins are ideal anticoagulants for most patients with thromboembolic disease in pregnancy as they do not cross the placenta and therefore the risk of fetal bleeding or teratogenicity is low. Low molecular weight heparin (eg, enoxaparin) is the preferred therapy, with patients transitioned to unfractionated heparin at term.

References

- VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.

Pharmacology	Pulmonary & Critical Care	Venous thromboembolism
Subject	System	Topic

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A 32-year-old woman is brought to the emergency department due to severe shortness of breath. She has no chest pain. The patient does not use tobacco. Temperature is 36.7 C (98 F), blood pressure is 132/81 mm Hg, pulse is 102/min, and respirations are 30/min. During physical examination, her condition deteriorates and she is emergently intubated due to acute respiratory failure. Shortly after intubation, she goes into cardiac arrest and dies despite resuscitation efforts. Review of the patient's medical records shows that she had been prescribed multiple medications but had a history of noncompliance. Autopsy shows hyperinflated lungs, airway mucus plugging, and cellular infiltration of the bronchial wall. Long-term use of which of the following drugs would have best prevented the cellular reaction in this patient's airways?

A. Albuterol
B. Fluticasone
C. Ipratropium
D. Magnesium sulfate
E. Montelukast
F. Theophylline

Submit

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- A. Albuterol (7%)
- ✓ B. Fluticasone (57%)
- C. Ipratropium (11%)
- D. Magnesium sulfate (0%)
- E. Montelukast (18%)
- F. Theophylline (3%)

Omitted
Correct answer
B

57%
Answered correctly

01 sec
Time Spent

04/05/2020
Last Updated

Explanation

This patient's autopsy findings of lung hyperinflation and bronchial inflammation are suggestive of **uncontrolled asthma**, a disease characterized by chronic airway inflammation, airway hyperresponsiveness, and intermittent bronchoconstriction. **Chronic inflammation**, composed mainly of **eosinophils**, helper T cells, and mast cells, causes airway remodeling (ie, bronchial wall thickening, **increased smooth muscle**), which further

This patient's autopsy findings of lung hyperinflation and bronchial inflammation are suggestive of **uncontrolled asthma**, a disease characterized by chronic airway inflammation, airway hyperresponsiveness, and intermittent bronchoconstriction. **Chronic inflammation**, composed mainly of **eosinophils**, helper T cells, and mast cells, causes airway remodeling (ie, bronchial wall thickening, **increased smooth muscle**), which further worsens airway obstruction and asthma symptoms.

Corticosteroids inhibit the production of inflammatory mediators (eg, cytokines, prostaglandins, leukotrienes), reduce leukocyte extravasation into the respiratory epithelium, and induce apoptosis of inflammatory cells. In addition, corticosteroids decrease smooth muscle proliferation and mucus production by goblet cells.

Systemic corticosteroids (eg, oral prednisone) are used in short courses to treat acute asthma exacerbations, whereas inhaled corticosteroids (eg, **fluticasone**) reduce the frequency and severity of exacerbations and are used for long-term asthma control in patients with persistent symptoms. Suppression of airway inflammation is evident within hours of administration but reaches maximal effect after several months of inhaled therapy. Nonadherence to long-term therapy can increase the risk of life-threatening asthma exacerbation.

(Choices A and C) Albuterol is a selective beta-2 adrenergic agonist that induces bronchodilation. Acetylcholine released through vagal stimulation mediates bronchoconstriction via muscarinic receptors on bronchial smooth muscle cells; ipratropium is a muscarinic antagonist that promotes bronchodilation and reduced mucus production. Neither of these agents has anti-inflammatory properties, and although short-acting beta agonists are widely used to provide rapid relief of symptoms during an exacerbation, they do not prevent inflammation-induced airway remodeling or alter the chronic disease course.

(Choice D) Magnesium sulfate inhibits calcium influx into airway smooth muscle and promotes bronchodilation when given intravenously during an acute asthma flare-up. Magnesium also reduces inflammation by stabilizing T cells and inhibiting mast cell degranulation; however, it is less effective than corticosteroids.

(Choice E) Leukotrienes are potent inducers of airway bronchoconstriction and inflammation. Leukotriene inhibitors (eg, montelukast) are useful for long-term control in some patients with asthma. However, they possess less efficacy and have fewer anti-inflammatory properties than inhaled glucocorticoids.

(Choice F) Theophylline, a phosphodiesterase inhibitor, results in increased intracellular cyclic AMP, which contributes to its role as a bronchodilator. Theophylline also has anti-inflammatory effects, although they are far less potent than glucocorticoids.

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(Choice F) Theophylline, a phosphodiesterase inhibitor, results in increased intracellular cyclic AMP, which contributes to its role as a bronchodilator. Theophylline also has anti-inflammatory effects, although they are far less potent than glucocorticoids.

Educational objective:
Asthma is characterized by chronic airway inflammation, which leads to airway remodeling, airway hyperresponsiveness, and bronchoconstriction. Corticosteroids reduce airway inflammation and are used for both chronic asthma management (inhaled administration) and acute exacerbations (systemic administration).

Pharmacology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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A 63-year-old man with a history of chronic obstructive pulmonary disease comes to the physician for a follow-up visit. He uses a tiotropium inhaler daily and his pulmonary symptoms are sufficiently controlled. During a previous visit, he was counseled on the benefits of smoking cessation. He reports that despite trying he has been unable to stop smoking due to overwhelming cravings. The physician prescribes a drug that reduces nicotine cravings while decreasing the pleasurable effects of cigarettes and other tobacco products. Which of the following medications was most likely prescribed to the patient?

A. Clonazepam

B. Fluoxetine

C. Nicotine patch

D. Topiramate

E. Varenicline

Submit

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- A. Clonazepam (3%)
- B. Fluoxetine (6%)
- C. Nicotine patch (15%)
- D. Topiramate (9%)
- ✓ E. Varenicline (64%)

Omitted
Correct answer
E

64%
Answered correctly

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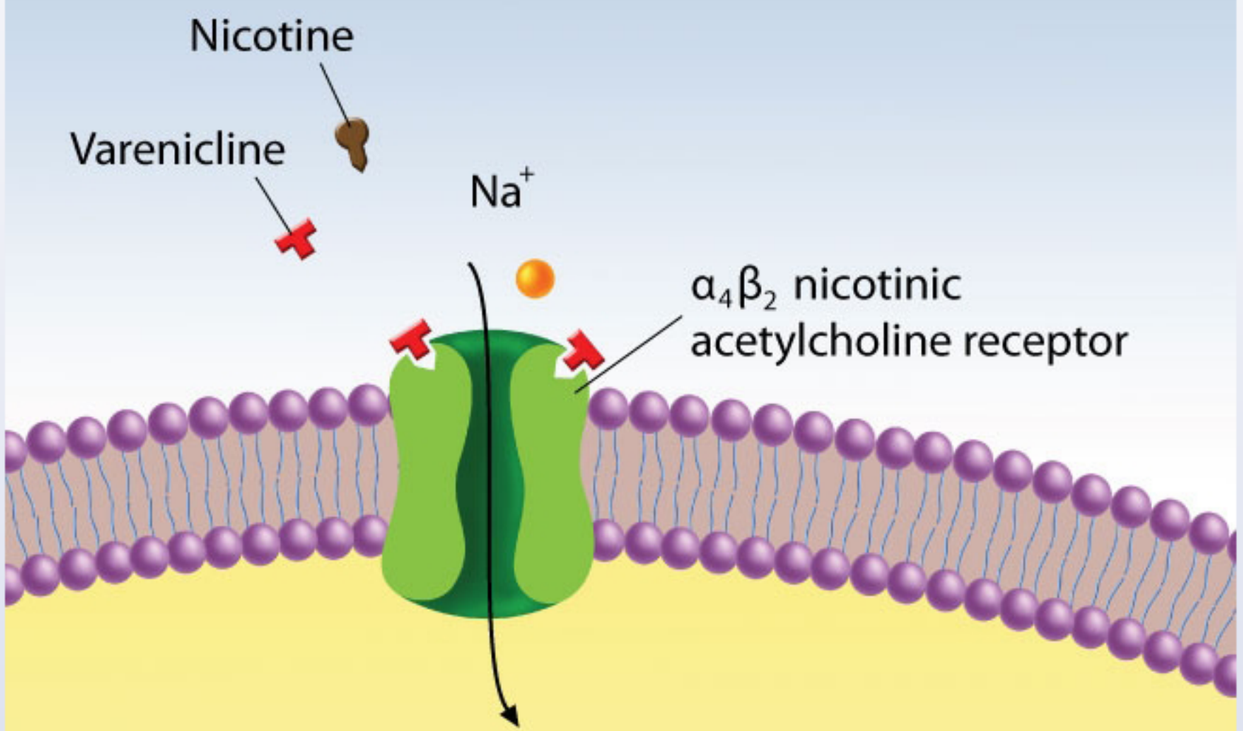
Time Spent

03/09/2020
Last Updated

Explanation

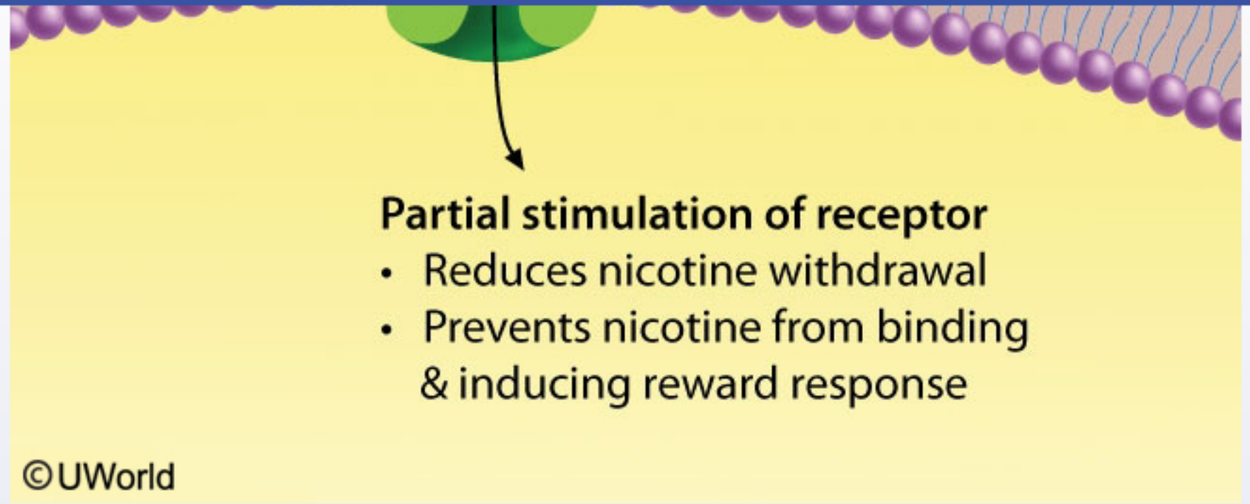
Mechanism of action of varenicline

Mechanism of action of varenicline



Partial stimulation of receptor

- Reduces nicotine withdrawal
- Prevents nicotine from binding & inducing reward response



The reinforcing effects of nicotine that lead to dependence are thought to be caused by stimulation of the $\alpha_4\beta_2$-nicotinic acetylcholine receptor present in the central nervous system. Varenicline is a partial agonist of this receptor that competes with nicotine (a full agonist) and prevents it from binding. Because varenicline is a partial agonist, it helps reduce the symptoms of nicotine withdrawal by mildly stimulating the receptor. Its partial agonist activity only causes limited downstream release of dopamine, resulting in less stimulation of the reward pathways than nicotine **(Choice C)**. Varenicline can thus assist patients with cessation of tobacco use by reducing withdrawal cravings and attenuating the rewarding effects of nicotine.

(Choices A and B) Selective serotonin reuptake inhibitors (eg, fluoxetine) and benzodiazepines (eg, clonazepam) have not been shown to be effective for smoking cessation.

(Choice D) Topiramate is an anticonvulsant used to treat epilepsy in children and adults. Topiramate is also an effective medication for migraine prophylaxis. However, it is not used for smoking cessation.

Educational objective:
Varenicline is a **partial agonist** of nicotinic acetylcholine receptors. It can assist patients with cessation of tobacco use by reducing withdrawal cravings and attenuating the rewarding effects of nicotine.

Partial stimulation of receptor

- Reduces nicotine withdrawal
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Pharmacology	Pulmonary & Critical Care	Smoking Cessation
Subject	System	Topic

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A 78-year-old woman is brought to the hospital due to 2 days of nausea, vomiting, abdominal pain, and headache. She was recently hospitalized due to a stroke, and the hospitalization was complicated by a urinary tract infection and delirium. The patient has a history of chronic obstructive pulmonary disease and her treatment regimen includes theophylline. Temperature is 37 C (98.6 F), blood pressure is 110/70 mm Hg, pulse is 118/min, and respirations are 22/min. On physical examination, the patient appears agitated and restless. There is a coarse tremor of the outstretched arms. Chest auscultation reveals mild expiratory wheezing. Serum theophylline levels are markedly elevated. Treatment with which of the following agents most likely precipitated this patient's current symptoms?

A. Amoxicillin
B. Cephalexin
C. Ciprofloxacin
D. Haloperidol
E. Nitrofurantoin

Submit

A 78-year-old woman is brought to the hospital due to 2 days of nausea, vomiting, abdominal pain, and headache. She was recently hospitalized due to a stroke, and the hospitalization was complicated by a urinary tract infection and delirium. The patient has a history of chronic obstructive pulmonary disease and her treatment regimen includes theophylline. Temperature is 37 C (98.6 F), blood pressure is 110/70 mm Hg, pulse is 118/min, and respirations are 22/min. On physical examination, the patient appears agitated and restless. There is a coarse tremor of the outstretched arms. Chest auscultation reveals mild expiratory wheezing. Serum theophylline levels are markedly elevated. Treatment with which of the following agents most likely precipitated this patient's current symptoms?

- A. Amoxicillin (5%)
- B. Cephalexin (4%)
- ✓ C. Ciprofloxacin (57%)
- D. Haloperidol (16%)
- E. Nitrofurantoin (15%)

Omitted
Correct answer
C

57%
Answered correctly

01 sec
Time Spent

02/07/2020
Last Updated

Explanation

Cytochrome P450 (CYP450) interactions	
Inducers	**Inhibitors**
	Alcohol (acute use)

Cytochrome P450 (CYP450) interactions

Inducers	Inhibitors
Alcohol (chronic use) Barbiturates (eg, phenobarbital) Carbamazepine Griseofulvin Modafinil Phenytoin Rifampin St. John's wort	Alcohol (acute use) Amiodarone Azoles (eg, fluconazole) Cimetidine Diltiazem, verapamil Grapefruit juice Isoniazid, macrolides,* quinolones Protease inhibitors (eg, ritonavir) SSRIs (eg, fluoxetine)
Drugs commonly affected Antiepileptics, theophylline, warfarin	

SSRIs = selective serotonin reuptake inhibitors.

*Except azithromycin.

This patient was most likely treated with **ciprofloxacin** (a fluoroquinolone) for her urinary tract infection and experienced subsequent **theophylline toxicity**. Theophylline is an adenosine receptor antagonist and phosphodiesterase inhibitor that is sometimes used as an alternate therapy for asthma and chronic obstructive pulmonary disease. It causes bronchodilation primarily by increasing intracellular cyclic AMP levels (similar to beta-adrenergic agonists) and also has mild anti-inflammatory effects.

Theophylline is metabolized predominantly by **hepatic cytochrome oxidases**. **Inhibition** of these enzymes by concurrent illness (eg, infection with fever) or ingestion of certain drugs or substances (eg, ciprofloxacin) can **raise serum concentrations** and cause theophylline toxicity due to the drug's narrow therapeutic index. Toxicity presents with excessive CNS stimulation (eg, tremor, insomnia, **seizures**), gastrointestinal disturbances, and cardiovascular abnormalities (eg, hypotension, tachycardia, **cardiac arrhythmias**).

(Choices A, B, and E) Amoxicillin and cephalexin are beta-lactams that inhibit bacterial cell wall synthesis. Nitrofurantoin inactivates or alters bacterial ribosomal proteins to inhibit protein and cell wall synthesis. These antibiotics do not interact significantly with the hepatic cytochrome

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(Choice D) Haloperidol blocks postsynaptic dopamine (D2) receptors in the brain but does not interact significantly with theophylline to cause toxicity. Chronic haloperidol use can cause neuroleptic malignant syndrome presenting with fever, mental status changes, muscle rigidity, and autonomic instability.

Educational objective:
Theophylline is an adenosine receptor antagonist and indirect adrenergic agent with a narrow therapeutic index. It is predominantly metabolized by the hepatic cytochrome oxidases. Inhibition of these enzymes by concurrent illness (eg, infection with fever) or ingestion of certain drugs or substances (eg, ciprofloxacin) can raise serum theophylline concentrations and cause toxicity (eg, seizures, cardiac arrhythmias).

References

- Ciprofloxacin-induced theophylline toxicity: a population-based study.
- Pharmacokinetic drug interactions with theophylline.

Pharmacology	Pulmonary & Critical Care	Theophyline
Subject	System	Topic

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A 42-year-old woman is evaluated due to frequent episodes of shortness of breath, chest tightness, and cough. The patient has been hospitalized on several occasions because of these symptoms and recently required mechanical ventilation due to respiratory failure. She takes multiple inhaled and systemic medications. The patient does not use tobacco, alcohol, or illicit drugs. Physical examination reveals scattered expiratory wheezes in both lungs. Peak expiratory flow rate is decreased from baseline. The treatment regimen is expanded to include a monoclonal antibody that binds circulating IgE, with the resulting complexes being subsequently cleared by reticuloendothelial cells. This medication is most likely to help this patient through which of the following mechanisms?

A. Decreasing airway collagen deposition

B. Decreasing airway inflammation

C. Decreasing alveolar destruction

D. Increasing cyclic AMP–mediated smooth muscle relaxation

E. Increasing pulmonary vasodilation

Submit

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- A. Decreasing airway collagen deposition (1%)
- ✓ B. Decreasing airway inflammation (82%)
- C. Decreasing alveolar destruction (5%)
- D. Increasing cyclic AMP–mediated smooth muscle relaxation (6%)
- E. Increasing pulmonary vasodilation (4%)

Omitted
Correct answer
B

82%
Answered correctly

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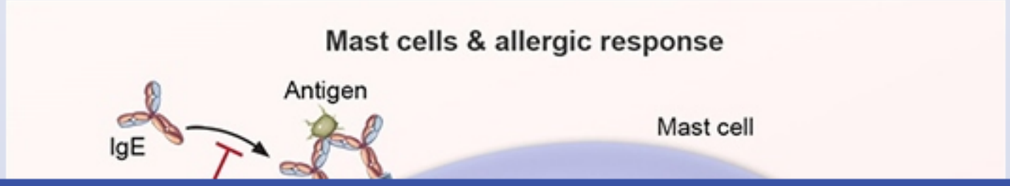
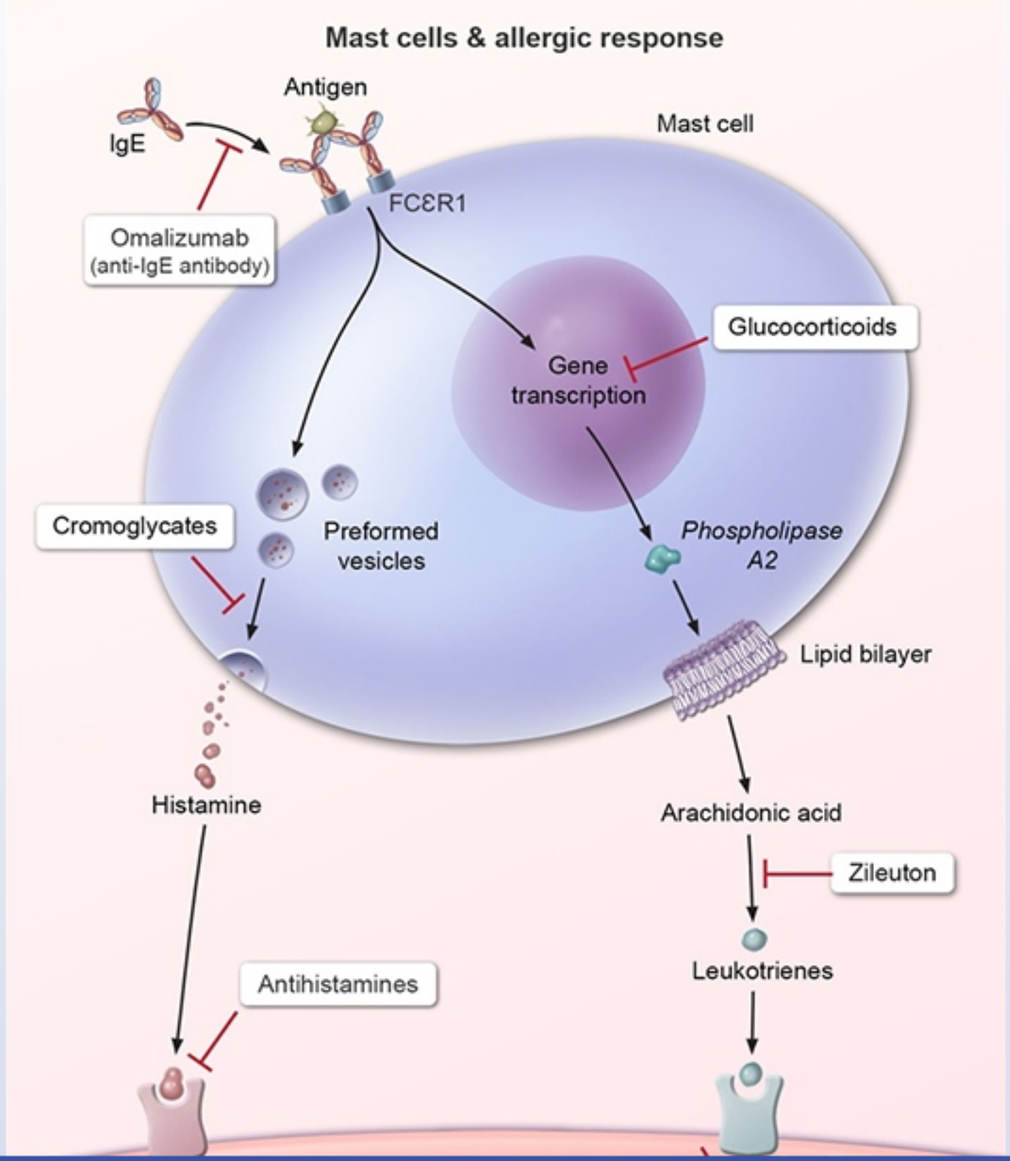
Time Spent

06/20/2020
Last Updated

Explanation




Mast cells & allergic response
Antigen
IgE
Mast cell
FCεR1
Omalizumab
(anti-IgE antibody)
Glucocorticoids
Gene
transcription
Cromoglycates
Preformed
vesicles
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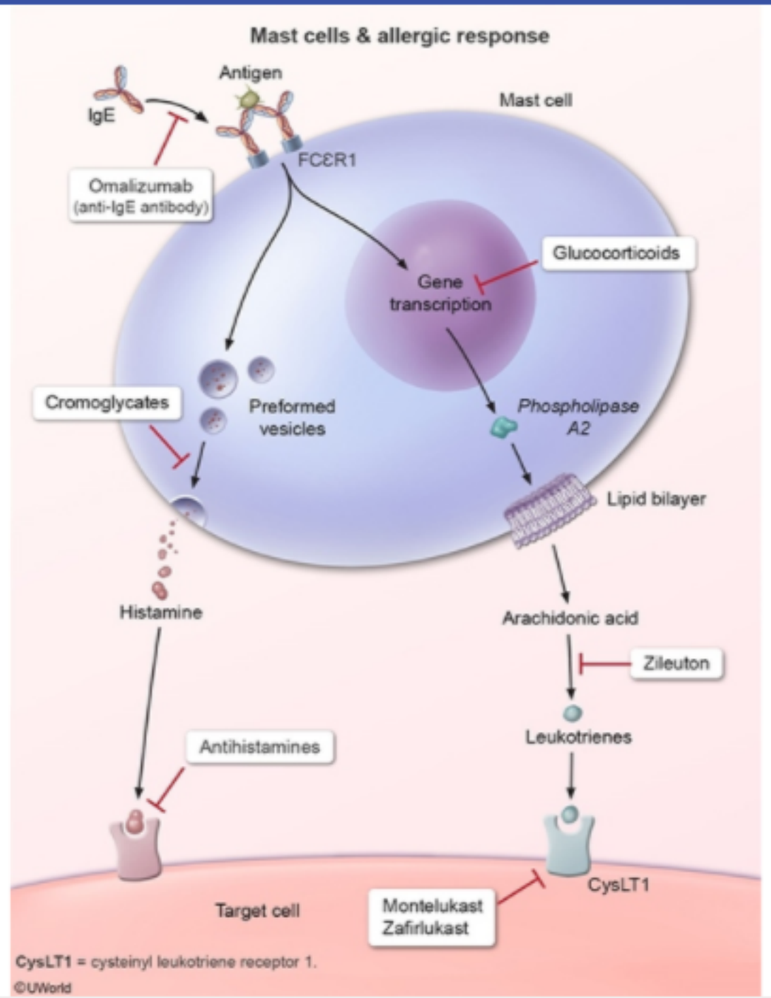
A2
Lipid bilayer
Histamine
Arachidonic acid
Zileuton
Leukotrienes
Antihistamines

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

This patient's frequent episodes of shortness of breath, chest tightness, and cough complicated by respiratory failure requiring hospitalization is consistent with **asthma**. The mainstays of medication therapy for asthma include an as-needed short-acting beta agonist (eg, albuterol), an inhaled corticosteroid (eg, mometasone), and a long-acting beta agonist (eg, salmeterol). For patients whose symptoms remain uncontrolled after such therapy is optimized, the addition of an **IgE-binding monoclonal antibody** (eg, omalizumab) may be beneficial.

Many patients with asthma have high levels of circulating IgE antibodies generated against environmental antigens (eg, dust mites, animal dander). Omalizumab binds to the IgE antibody heavy chain and blocks the binding of IgE to the IgE receptors on mast cells. By preventing this binding, omalizumab **inhibits proinflammatory substance release** (including histamine and leukotrienes) by mast cells, markedly **reducing airway inflammation**.

(Choice A) Decreasing airway collagen deposition may help slow the progression of idiopathic pulmonary fibrosis (IPF). Certain tyrosine kinase inhibitors (eg, nintedanib) decrease fibroblast proliferation and have shown benefit in treating IPF.

(Choice C) Decreasing alveolar destruction would be helpful in treating chronic obstructive pulmonary disease (COPD). Smoking cessation is the most effective way to prevent and/or slow the rate of progression of COPD.

(Choice D) Beta-2 agonists (eg, albuterol, salmeterol) cause bronchodilation via cyclic AMP–mediated smooth muscle relaxation and are effective symptomatic treatments for asthma. These drugs do not significantly reduce airway inflammation.

(Choice E) Increasing pulmonary vasodilation helps improve pulmonary arterial hypertension and can be achieved with several classes of drugs, including endothelin receptor antagonists (eg, bosentan), phosphodiesterase inhibitors (eg, sildenafil), and prostacyclin analogs.

Educational objective:
IgE-binding monoclonal antibodies (eg, omalizumab) are effective in treating asthma that remains uncontrolled despite optimal therapy with bronchodilators and inhaled corticosteroids. IgE-binding monoclonal antibodies reduce airway inflammation by blocking the binding of IgE to the IgE receptors on mast cells and preventing the release of proinflammatory substances, including histamine and leukotrienes.

References

- Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma.
- Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review.

A 65-year-old man comes to the office due to a 6-month history of exertional dyspnea. Over the past few weeks he has also developed a nonproductive cough. Medical history is notable for hypertension and hypercholesterolemia. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.9 C (98.4 F), blood pressure is 130/80 mm Hg, pulse is 80/min, and respirations are 18/min. Examination shows late inspiratory crackles in both lung bases and mild digital clubbing. The patient undergoes lung biopsy; histologic examination shows areas of interstitial inflammation, foci of proliferating fibroblasts, dense collagen fibrosis, and honeycomb changes. The interstitial inflammation is patchy and consists of a lymphoplasmacytic infiltrate in the alveolar septa associated with hyperplasia of type 2 pneumocytes. Pharmacotherapy aimed at which of the following is most helpful in treating this patient's lung condition?

A. Alpha-1 antitrypsin
B. Endothelin-1
C. Interleukin-5
D. Phosphodiesterase-4
E. Transforming growth factor beta

Submit

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A. Alpha-1 antitrypsin (10%)

B. Endothelin-1 (16%)

C. Interleukin-5 (5%)

D. Phosphodiesterase-4 (5%)

✓ E. Transforming growth factor beta (61%)

Omitted
Correct answer
E

61%
Answered correctly

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Time Spent

03/02/2020
Last Updated

Explanation

This patient with progressive dyspnea, dry cough, digital clubbing, and crackles on examination has signs of an interstitial lung disease. The histologic findings of patchy **lymphoplasmacytic infiltrates**, focal fibroblastic proliferation, areas of dense fibrosis and honeycombing, and hyperplasia of type 2 pneumocytes are highly suggestive of **idiopathic pulmonary fibrosis** (IPF).

Explanation

This patient with progressive dyspnea, dry cough, digital clubbing, and crackles on examination has signs of an interstitial lung disease. The histologic findings of patchy **lymphoplasmacytic infiltrates**, focal fibroblastic proliferation, areas of dense fibrosis and honeycombing, and hyperplasia of type 2 pneumocytes are highly suggestive of **idiopathic pulmonary fibrosis** (IPF).

IPF is a chronic, progressive fibrotic lung disease thought to be due to recurrent episodes of lung injury and disordered healing. Persistent inflammation likely triggers excessive activity of growth factors normally involved in wound healing, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), fibroblastic growth factor (FGF), and vascular endothelial growth factor (VEGF). This leads to increased fibroblast activity, myofibroblast formation, and collagen production, which contribute to pulmonary fibrosis. **Pirfenidone** is an antifibrotic agent that **inhibits TGF-β**; another treatment option is nintedanib, a tyrosine kinase inhibitor that inhibits PDGF, FGF, and VEGF. Although neither drug is curative, these therapies have been shown to slow progressive fibrosis in patients with IPF.

(Choice A) Alpha-1 antitrypsin infusion is used to treat patients with alpha-1 antitrypsin deficiency, which causes panacinar emphysema and typically presents in young patients with dyspnea and cough. Histologic findings in emphysema include large alveoli with thin septa.

(Choice B) Endothelin-1 inhibitors (eg, ambrisentan, bosentan) are used to treat idiopathic pulmonary hypertension. Histologic findings of pulmonary hypertension include pulmonary vascular media and intima hypertrophy and intimal fibrosis.

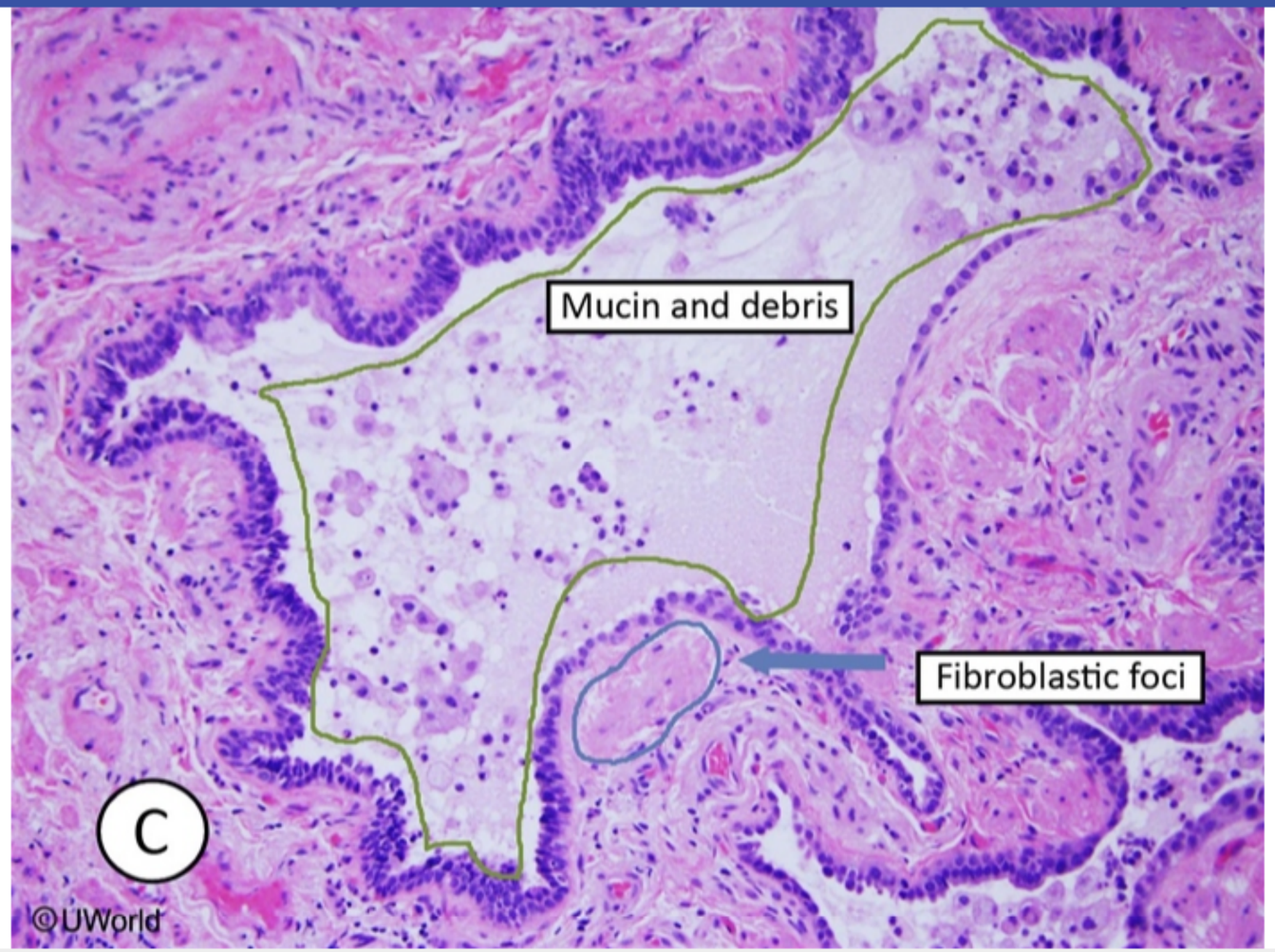
(Choice C) Monoclonal antibodies directed at interleukin-5 (eg, reslizumab) inhibit eosinophil recruitment and proliferation, and are used in patients with severe eosinophilic asthma. Histologic findings in asthma include goblet cell hyperplasia, bronchial smooth muscle hypertrophy, edema, eosinophilia, and Charcot-Leyden crystals.

(Choice D) Phosphodiesterase-4 inhibitors (ie, roflumilast) block the degradation of cyclic AMP, leading to reduced airway inflammation and smooth muscle relaxation in patients with chronic obstructive pulmonary disease. Histologic findings include both airspace enlargement with thin septa (emphysema) and goblet cell hyperplasia with excess mucus production (chronic bronchitis).

Educational objective:
Histologic findings of idiopathic pulmonary fibrosis include patchy lymphoplasmacytic infiltrates, focal fibroblastic proliferation with dense fibrosis, honeycombing, and hyperplasia of type 2 pneumocytes. Therapies are directed at slowing the progression of fibrosis by inhibiting transforming growth factor-beta and other fibrogenic growth factors (eg, PDGF, fibroblastic growth factor, and VEGF).

Explanation

Exhibit Display



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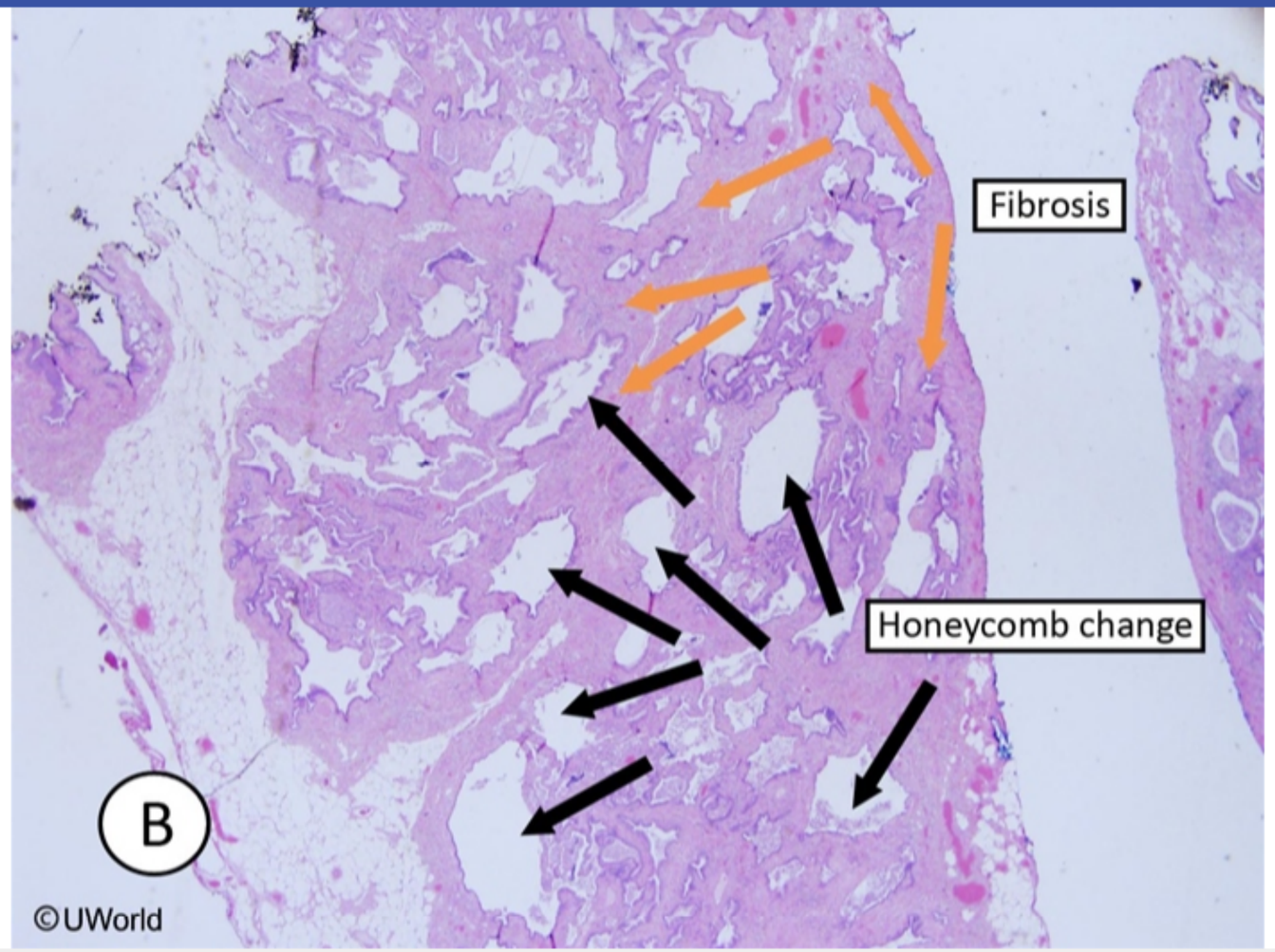
growth factor beta and other fibrogenic growth factors (eg, PDGF, fibroblastic growth factor, and VEGF).

Explanation

Exhibit Display



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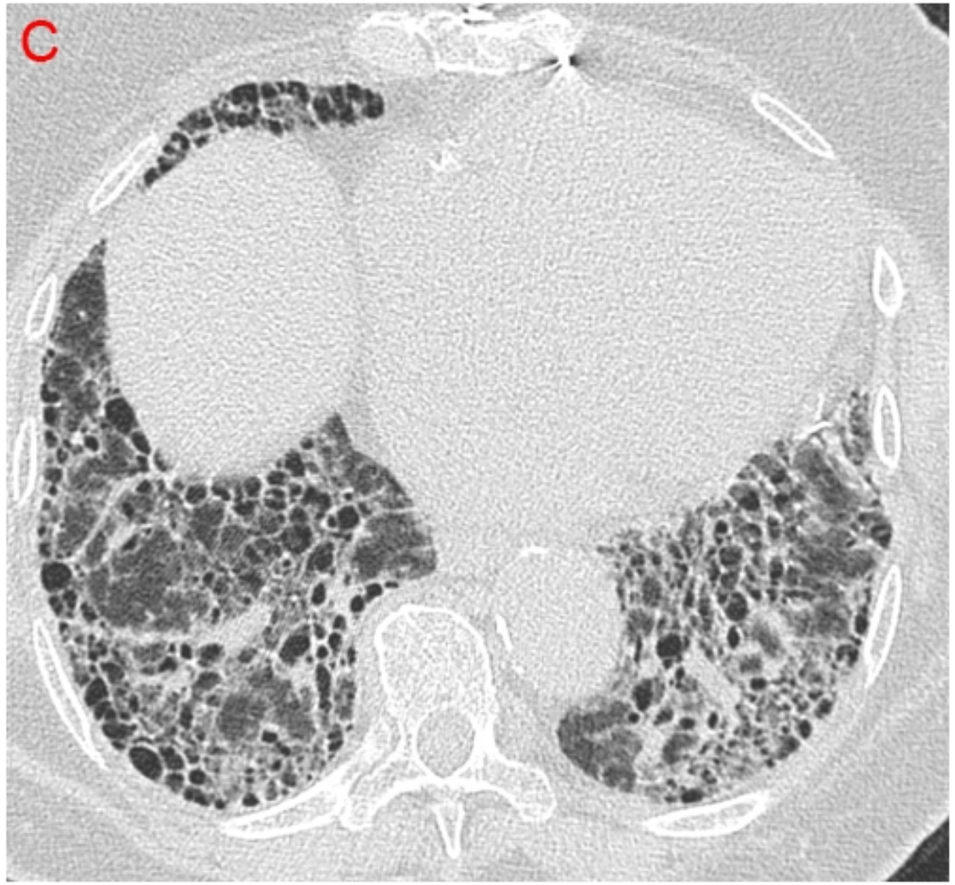

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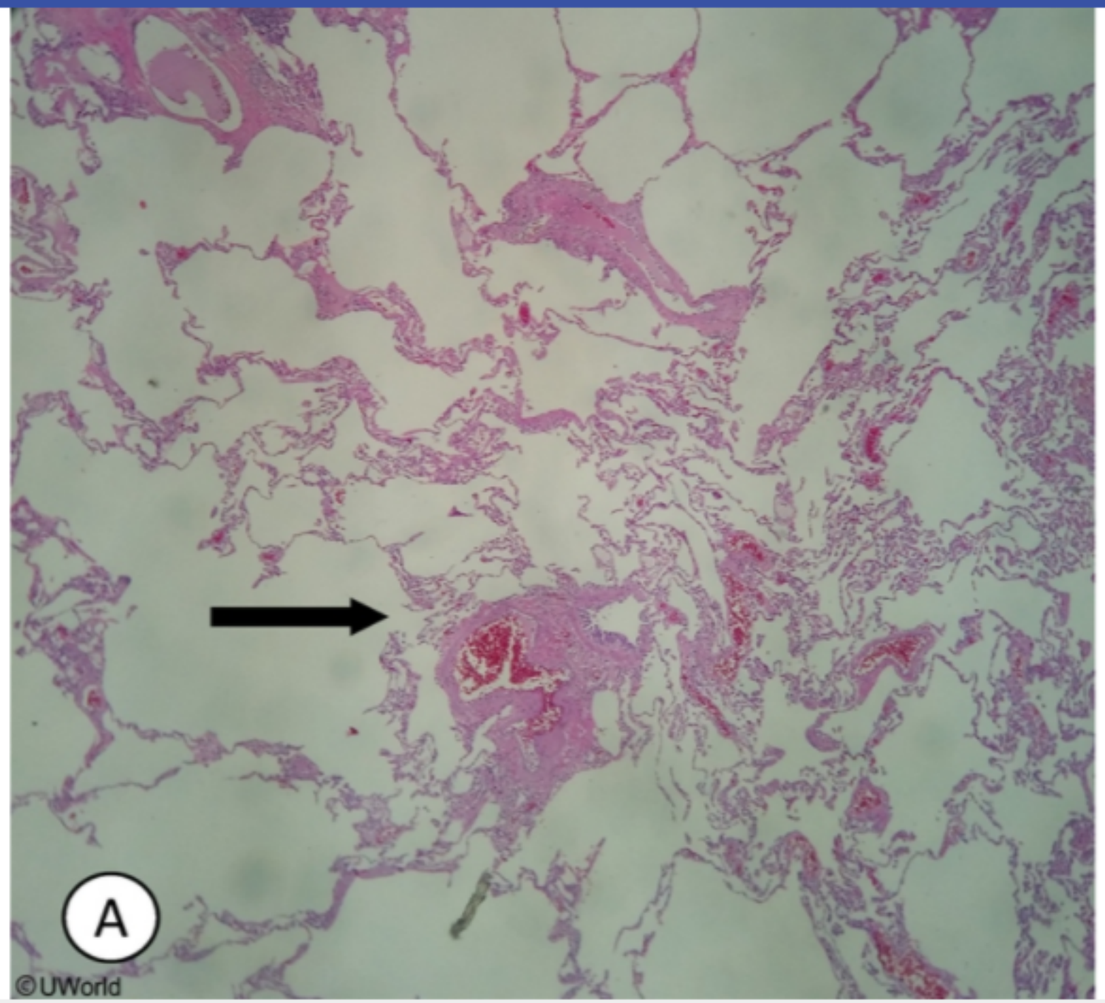

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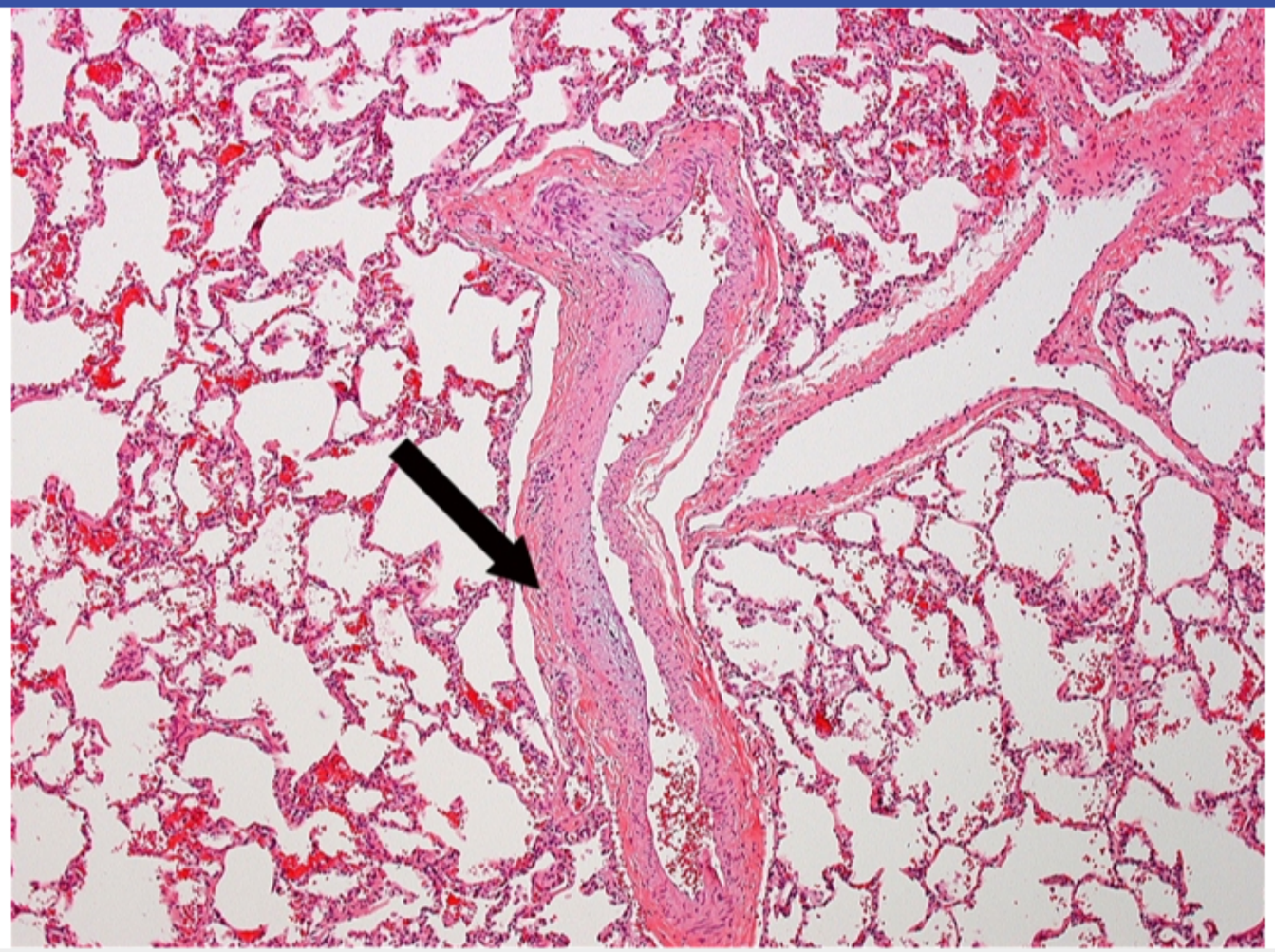

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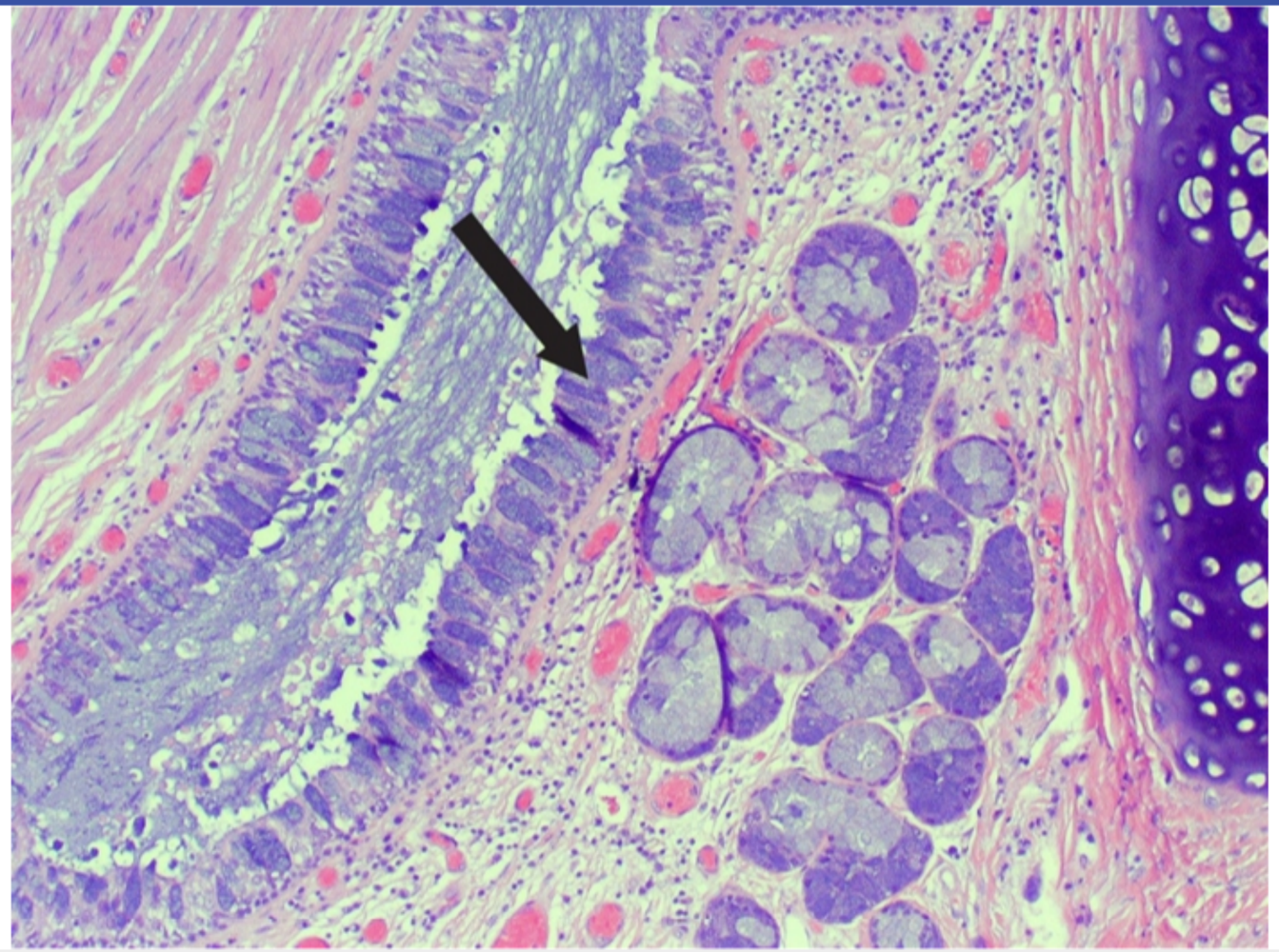

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IPF is a chronic, progressive fibrotic lung disease thought to be due to recurrent episodes of lung injury and disordered healing. Persistent inflammation likely triggers excessive activity of growth factors normally involved in wound healing, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), fibroblastic growth factor (FGF), and vascular endothelial growth factor (VEGF). This leads to increased fibroblast activity, myofibroblast formation, and collagen production, which contribute to pulmonary fibrosis. **Pirfenidone** is an antifibrotic agent that **inhibits TGF-β**; another treatment option is nintedanib, a tyrosine kinase inhibitor that inhibits PDGF, FGF, and VEGF. Although neither drug is curative, these therapies have been shown to slow progressive fibrosis in patients with IPF.

(Choice A) Alpha-1 antitrypsin infusion is used to treat patients with alpha-1 antitrypsin deficiency, which causes panacinar emphysema and typically presents in young patients with dyspnea and cough. Histologic findings in emphysema include large alveoli with thin septa.

(Choice B) Endothelin-1 inhibitors (eg, ambrisentan, bosentan) are used to treat idiopathic pulmonary hypertension. Histologic findings of pulmonary hypertension include pulmonary vascular media and intima hypertrophy and intimal fibrosis.

(Choice C) Monoclonal antibodies directed at interleukin-5 (eg, reslizumab) inhibit eosinophil recruitment and proliferation, and are used in patients with severe eosinophilic asthma. Histologic findings in asthma include goblet cell hyperplasia, bronchial smooth muscle hypertrophy, edema, eosinophilia, and Charcot-Leyden crystals.

(Choice D) Phosphodiesterase-4 inhibitors (ie, roflumilast) block the degradation of cyclic AMP, leading to reduced airway inflammation and smooth muscle relaxation in patients with chronic obstructive pulmonary disease. Histologic findings include both airspace enlargement with thin septa (emphysema) and goblet cell hyperplasia with excess mucus production (chronic bronchitis).

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Histologic findings of idiopathic pulmonary fibrosis include patchy lymphoplasmacytic infiltrates, focal fibroblastic proliferation with dense fibrosis, honeycombing, and hyperplasia of type 2 pneumocytes. Therapies are directed at slowing the progression of fibrosis by inhibiting transforming growth factor-beta and other fibrogenic growth factors (eg, PDGF, fibroblastic growth factor, and VEGF).

Pharmacology	Pulmonary & Critical Care	Interstitial lung disease
Subject	System	Topic

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A 63-year-old man hospitalized for chronic obstructive pulmonary disease exacerbation develops hypercapnic respiratory failure. He is transferred to the intensive care unit, where he undergoes intubation after premedication with muscle relaxant X and an appropriate sedative. The patient is then started on mechanical ventilation; however, he remains apneic longer than expected. Anesthesiology is consulted, and the patient's neuromuscular blockade is assessed by electrically stimulating a peripheral nerve 4 times in quick succession and observing the muscular response. The procedure is repeated 30 minutes later and the results are shown below.

Muscle relaxant X is most likely to be which of the following medications?

A. Dantrolene
B. Midazolam
C. Pancuronium
D. Succinylcholine
E. Tubocurarine

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Muscle relaxant X is most likely to be which of the following medications?

A. Dantrolene (6%)
B. Midazolam (4%)
C. Pancuronium (10%)
✓ D. Succinylcholine (71%)
E. Tubocurarine (7%)

Omitted
Correct answer

71%
Answered correctly

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Time Spent

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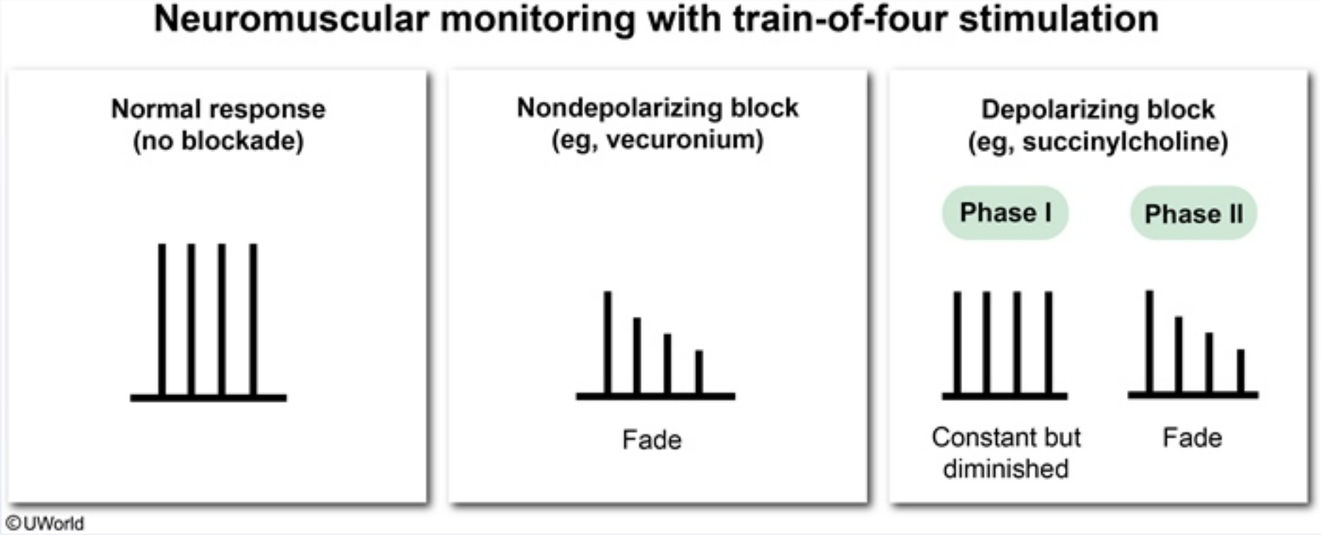
Last Updated



Train-of-four (TOF) stimulation is used during anesthesia to assess the degree of paralysis induced by neuromuscular junction (NMJ)-blocking agents. A peripheral nerve is stimulated 4 times in quick succession and the muscular response is recorded. The height of each bar represents the strength of each twitch; higher bars indicate the activation of increasing numbers of individual muscle fibers (myocytes).

When a **nondepolarizing NMJ blocker** (eg, vecuronium) is administered, competitive inhibition of postsynaptic acetylcholine receptors at the motor endplate prevents some of these fibers from activating, decreasing the strength of the twitch. TOF stimulation shows a **progressive reduction** in each of the 4 responses (fading pattern) as a result of less acetylcholine being released with each subsequent impulse (due to the additional effect of presynaptic acetylcholine receptor blockade). In contrast, **depolarizing blockers** (eg, **succinylcholine**) initially function by preventing repolarization of the motor endplate and show **equal reduction** of all 4 twitches during TOF stimulation **(phase I blockade)**. The responses remain equal because the presynaptic acetylcholine receptor stimulation helps to mobilize presynaptic acetylcholine vesicles for release. Persistent exposure to succinylcholine results in eventual transition to **phase II blockade** as the acetylcholine receptors become desensitized and inactivated (ie, functionally similar to nondepolarizing blockade).

Succinylcholine is commonly administered for **rapid-sequence intubation** due to its rapid onset (<1 minute). The duration of action is determined by its metabolism by plasma cholinesterase and is typically <10 minutes. However, some patients are homozygous for an atypical plasma

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Succinylcholine is commonly administered for **rapid-sequence intubation** due to its rapid onset (<1 minute). The duration of action is determined by its metabolism by plasma cholinesterase and is typically <10 minutes. However, some patients are homozygous for an atypical plasma cholinesterase, which breaks down succinylcholine more slowly. In these patients, the paralysis can last for **hours** and they must be maintained on mechanical ventilation until spontaneous respirations resume.

(Choice A) Dantrolene relaxes skeletal muscle by reducing the release of Ca^{2+} from the sarcoplasmic reticulum. Dantrolene is used to treat malignant hyperthermia and neuroleptic malignant syndrome. It is not routinely used as a neuromuscular paralytic agent.

(Choice B) Benzodiazepines are effective for sedation, but they have no direct action at the NMJ and do not provide sufficient muscle paralysis to facilitate intubation.

(Choices C and E) Pancuronium and tubocurarine are nondepolarizing NMJ blockers. Unlike depolarizing NMJ drugs, these agents do not function in distinct phases and their TOF responses always display a fading pattern. Neostigmine administration reverses nondepolarizing NMJ blockade.

Educational objective:
Succinylcholine is a fast-acting, depolarizing neuromuscular blocking agent used for rapid-sequence intubation that causes equal reduction of all 4 twitches during train-of-four stimulation (phase I blockade). Prolonged administration of succinylcholine or use in patients with abnormal plasma

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Educational objective:
Succinylcholine is a fast-acting, depolarizing neuromuscular blocking agent used for rapid-sequence intubation that causes equal reduction of all 4 twitches during train-of-four stimulation (phase I blockade). Prolonged administration of succinylcholine or use in patients with abnormal plasma cholinesterase activity causes transition to a phase II (nondepolarizing) block, seen as a progressive reduction in each of the 4 twitches.

Pharmacology	Pulmonary & Critical Care	Neuromuscular blocker
Subject	System	Topic

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